

■ COVER STORY

From The Endocrine Society's Research Affairs Core Committee  
Edited by Kerry Burnstein, Ph.D.

# Finding New Directions in





# Prostate Cancer

Just as prostate cancers have variable characteristics, so should treatments. Patients with early forms of this disease have several options, namely surgery, radiation, and chemotherapy, but the choices narrow later for those with castration-resistant prostate cancers (CRPC). In this Tri-Point article, a clinician, a basic scientist, and a clinical researcher discuss the latest treatment advances for cancers in this organ.

## Clinical Practitioner Perspective

By Ana Aparicio, M.D.



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## Highlights

- Active surveillance is a valid “treatment” option for localized prostate tumors that carry a low lifetime risk of clinical progression.
- Secondary hormone manipulations are an effective treatment modality for CRPC.
- Several chemotherapy agents can provide significant palliation to men with CRPC, and two (docetaxel and cabazitaxel) improve survival.
- Sipuleucel-T, the first therapeutic vaccine approved by the U.S. FDA, improves the survival of men with asymptomatic or minimally symptomatic CRPC.

The first thing I tell patients when we meet is that although we give prostate cancer one name, it encompasses multiple, clinically distinct subsets, which we are only beginning to understand. Therefore, one size does not fit all when it comes to prostate cancer. In recent years, the treatment has undergone several paradigm changes that are taking us closer to a much needed, biologically based, predictive classification of the disease. Highlights include:

### 1. Not all prostate cancers need treatment: Active surveillance is a valid option.

Since the prostate-specific antigen (PSA) measurement was incorporated as a screening tool for prostate cancer, about 200,000 men have been diagnosed annually in

the United States. However, more than half might never develop clinical symptoms during their lifetimes and thus should be spared definitive treatments (typically surgery or radiation) that carry a significant risk for adverse events. Identifying those men who can eschew treatment has become one of the biggest challenges in the field. In the meantime, an active surveillance protocol, in which definitive treatment is reserved for evidence of tumor progression, is a valid option. This approach is appropriate for men diagnosed with localized prostate tumors that are unlikely to pose a threat to their quality or quantity of life.<sup>1</sup> However, the optimal method for active surveillance remains to be defined.

### 2. The AR remains the central driver of most CRPC.

The standard, first-line treatment for advanced prostate cancer is to deplete circulating levels of testosterone, generally via bilateral orchiectomies or the administration of luteinizing hormone–releasing hormone agonists or antagonists, which inhibit the production of testicular androgens. Although most prostate cancers respond to these forms of castration, within 18–24 months on average, the disease will progress despite low circulating testosterone levels.<sup>2</sup> For years, the cancer was called “androgen-independent,” despite the fact that responses were known to occur with secondary hormonal treatments, including antiandrogens (e.g., bicalutamide, nilutamide, or flutamide), the androgen biosynthesis inhibitor ketoconazole, and estrogens (e.g., diethylstilbestrol and conjugated estrogens). The realization that the androgen receptor (AR) remains at the center of most CRPC progression is producing not only significant insight into the biology of the disease but also important therapeutic advances.<sup>3</sup> Novel AR antagonists such as MDV3100 have been developed, as well as androgen biosynthesis inhibitors such as abiraterone. In a recent, phase III clinical trial, abiraterone improved median overall survival by 3.9 months in combination with prednisone, compared with prednisone alone, in men with CRPC previously treated with docetaxel chemotherapy.<sup>4</sup>

### 3. Chemotherapy works in prostate cancer.

Less than a decade ago, there was general skepticism that chemotherapy provided any substantial benefit to men with advanced prostate cancer. In 1996, mitoxantrone plus prednisone was reported to improve the quality of life of these men over prednisone alone, but not their median overall survival.<sup>5</sup> Then in 2004, docetaxel plus prednisone showed a 2–3 month median overall survival benefit in men with CRPC over mitoxantrone plus prednisone in two separate randomized trials.<sup>6,7</sup> More recently, in 2010, cabazitaxel plus prednisone showed a 2.4-month improvement in median overall survival compared with mitoxantrone plus prednisone in men with docetaxel-refractory CRPC.<sup>8</sup> Perhaps most importantly, these chemotherapy agents and others that have not undergone phase III clinical trial testing (i.e., paclitaxel, cyclophosphamide, the vinca alkaloids, carboplatin, etoposide, or doxorubicin) have shown activity<sup>9</sup> and can provide significant palliation to men with advanced CRPC. Therefore, chemotherapy has been definitively incorporated into the treatment armamentarium for these types of late cancers.

### 4. Immunotherapy also works in prostate cancer.

A long history of research into the use of immunotherapy for prostate cancer treatment recently began to yield fruitful and exciting results. Most notably, sipuleucel-T, an autologous active cellular immunotherapy, in randomized phase III trials prolonged median overall survival by 4.1 months in patients with metastatic asymptomatic or minimally symptomatic CRPC, leading to its approval by the U.S. Food and Drug Administration (FDA) in 2010.<sup>10</sup> Intriguingly, sipuleucel-T did not prolong the time to disease progression, leaving to speculation what mechanism lies behind the survival benefit.

In conclusion, significant advances have been made in the understanding of prostate cancer biology, resulting in numerous treatment modalities that give incremental benefits to men afflicted by this disease; thus they need incorporation into standard clinical practice.

## Basic Researcher Perspective

By Steve Balk, M.D., Ph.D.



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Advances over the past several years brought an unprecedented series of paradigm shifts in our understanding of prostate cancer biology and subsequent approaches to therapy. This brief overview summarizes therapeutically relevant advances in our understanding of prostate cancer pathogenesis and AR-targeted therapies for tumors that relapse after androgen deprivation (now called CRPC) therapies, and the new challenges that are emerging

## Highlights

- Gene rearrangements occur commonly during prostate cancer development, with about half of cases expressing the androgen-regulated *TMPRSS2:ERG* fusion gene.
- Many men with low-grade (Gleason Grade 3) tumors do not need therapy, but the natural history of these tumors is poorly understood.
- Increased intratumoral androgen synthesis contributes to AR reactivation in prostate cancers that relapses after androgen deprivation therapy (CRPC).
- Abiraterone, an inhibitor of CYP17A1, an enzyme required for androgen synthesis, improves survival in CRPC.
- New AR antagonists with novel mechanisms of action are being developed and show activity in CRPC.

as a result. The recent FDA approval of an autologous dendritic cell–based vaccine for CRPC is clearly another major advance, but is not discussed further here.

### Gene rearrangements contribute to prostate cancer development.

Although gene translocations/fusions are common in leukemias and lymphomas, these anomalies were thought not to play a role in any major epithelial cancers. A paradigm shift occurred in 2005 with the discovery that the *TMPRSS2* gene, which is androgen regulated and highly expressed in the prostate, is fused to *ERG* (an *Ets* family transcription factor) in approximately half of prostate cancers.<sup>1</sup> Fusions involving *TMPRSS2* or other androgen-regulated genes to other *Ets* genes or oncogenes are also observed, and a recent, whole genome sequencing study revealed that primary prostate cancers contain multiple gene translocations.<sup>2</sup> Current challenges are to understand the basis for this apparent genomic instability and to discover precisely how *ERG* overexpression drives prostate cancer development and/or progression.

### Many men diagnosed with prostate cancer have an indolent disease that does not need treatment.

As noted above, many men whose biopsies show only low-grade (Gleason Grade 3) prostate cancers have indolent disease that will not become clinically significant in their lifetimes and do not require aggressive therapy (i.e., radical prostatectomy or radiation). However, it is unclear which tumors can eventually progress to higher grades or what might serve as biomarkers for men at increased risk of developing more aggressive tumors. There are now pressing needs to determine whether subsets of these tumors are truly benign, to examine whether interventions exist that can delay/prevent progression, and to develop imaging or other approaches to safely monitor these lesions.

## AR in CRPC is reactivated and dependent on increased androgen synthesis by tumor cells (intratumoral androgen synthesis).

The vast majority of primary prostate cancers express high AR levels and respond to surgical/medical castration (androgen deprivation therapy), which remains the standard treatment for metastasized prostate cancers. For many years, scientists knew that tumors relapsing after this therapy invariably express high AR levels and that the AR gene is frequently amplified,<sup>3</sup> but efforts to improve responses by further suppressing AR activity using available AR antagonists have been largely unsuccessful. Therefore, this phase of the disease—CRPC—had been termed “hormone refractory,” with the AR’s role and the mechanisms driving its activity unknown.

Studies by several groups have now established that CRPC cells express increased levels of enzymes mediating the synthesis of potent androgens (testosterone and dihydrotestosterone, DHT) from the weak precursors made in the adrenal gland, which are present at high levels after castration (primarily dehydroepiandrosterone sulfate [DHEA-S]). These enzymes allow CRPC cells to generate potent androgens at levels that are at least equivalent to those prior to castration.<sup>4-6</sup> The importance of AR and of this mechanism for AR activation is supported by clinical trials showing responses in CRPC to ketoconazole, an inhibitor of the enzyme CYP17A1, which catalyzes two steps required for the conversion of pregnenolone/progesterone to the androgen precursors DHEA/androstenedione.<sup>7</sup> Significantly, this mechanism was recently confirmed in clinical trials of abiraterone, a more potent/specific CYP17A1 inhibitor that markedly decreases residual androgen levels and extends the survival of taxane-resistant CRPC patients.<sup>8</sup>

With its recent FDA approval, abiraterone will likely become the standard therapy for CRPC. New challenges facing researchers are to determine whether this drug might be more effective if used earlier or in combination with other agents, and to understand how tumors develop resistance to CYP17A1 inhibitors. These latter mechanisms may include: up-regulation of intratumoral CYP17A1 activity and increased de novo androgen synthesis; alterations in AR or associated proteins that enhance AR responses to alternative ligands upstream of CYP17A1; the generation of ligand-independent AR isoforms through alternative AR splicing that deletes the ligand binding domain; and/or mechanisms that circumvent the requirement for AR.

### New AR antagonists offer novel mechanisms of action.

Currently available AR antagonists, including bicalutamide, prevent AR recruitment of transcriptional coactivator proteins, but do not prevent AR binding to chromatin, and may acquire agonist activity in CRPC cells with alterations in transcriptional coactivator/corepressor proteins or in cells expressing high levels of AR.<sup>9</sup> MDV3100, a new AR antagonist that impairs AR nuclear localization/chromatin binding, has shown very promising activity in CRPC and is now in phase III clinical trials.<sup>9</sup> The success of MDV3100

has restored interest in AR antagonists that function by novel mechanisms through the AR C-terminal ligand binding domain. Moreover, a recent study identified small molecule inhibitors of the AR N-terminal transactivation domain that can suppress both wild-type and constitutively active, alternatively spliced ARs that have lost the ligand binding domain.<sup>10</sup> Overall, this new wave of agents presents an unprecedented opportunity to more effectively target AR in advanced CRPC, and to explore the effects of more aggressive androgen deprivation at earlier disease stages.

## Clinical Researcher Perspective

By William Kevin Kelly, D.O.



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### Highlights

- AR remains functionally active in CRPC patients.
- Multiple survival mechanisms evolve in prostate cancer cells when exposed to low androgen concentrations.
- Abiraterone acetate is a novel agent in the class of ABI that have clinical benefit in patients with CRPC.
- Multiple agents that target the C- or N-terminal ends of the AR or nuclear translocation of AR are being developed.
- There is a critical need for biomarkers to identify which patients are appropriate for these AR-directed therapies.

For 6 decades, surgical or medical castration has played a key role in advanced prostate cancer treatment, providing palliation, objective tumor regression, and in some cases prolonged survival. Subsequently, the concept of complete androgen blockade evolved with the development of the steroidal and non-steroidal antiandrogens (e.g., cyproterone acetate, flutamide, bicalutamide, and nilutamide). However, complete androgen blockade offered modest clinical benefit and patients progressed to CRPC with a median survival of only 12–18 months.<sup>1</sup> It was clear that understanding the pathways and mechanisms that underlie castration resistance development was critical for encouraging new therapeutic interventions. Investigators have now shown that the mechanisms responsible for the growth of CRPC are diverse and include AR mutations and alternative splicing in the AR, overexpression of AR and its co-regulators, intracrine synthesis of androgens by the prostate cancer, and ligand-independent AR signaling pathways.<sup>2</sup> These discoveries accelerated the

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development of several new therapies designed to modify AR activity in CRPC patients.

Abiraterone acetate is the first in the class of the androgen biosynthesis inhibitors (ABI) that target the intracrine synthesis of androgens. This agent is a selective, non-reversible inhibitor of the CYP17 enzymes (CYP17  $\alpha$ -hydroxylase and CYP17,20-lyase). Early studies showed that abiraterone acetate lowered the plasma concentrations of testosterone, DHEA, androstenedione, and estradiol to near non-detectable concentrations in patients.<sup>3,4</sup> The pivotal, randomized study showed that patients treated with abiraterone acetate (1,000 mg/day) and prednisone 5 mg BID had significant improvement in overall survival compared with the placebo and prednisone 5 mg BID (14.1 vs. 10.2 months, HR 0.646,  $P < 0.0001$ ) and was well tolerated.<sup>5</sup> TAK-700 or VN/124-1 (TOK-001) are two additional, novel, ABI undergoing clinical evaluation; they may have certain advantages over abiraterone acetate.<sup>6</sup> Other strategies to block the AR activity have focused on agents that target the AR's C-terminal domain. MDV3100 is a second generation, oral, small-molecule antagonist of the AR that prevents nuclear translocation and DNA binding of AR. Dose-escalation studies showed this agent to be well tolerated, and 56% of the patients had a decline in PSA during therapy and a third had radiographic tumor regression.<sup>7</sup> A concern for this class of agents has been the onset of seizures; however they have not been reported with MDV3100 at doses of 240 mg/day or less. Randomized studies are ongoing to determine the clinical benefit of this agent in CRPC.<sup>7</sup>

Several agents currently in pre-clinical development could also contribute to the CRPC treatment. SNARE-1 (selective nuclear receptor exporter 1) is a small molecule that binds AR and interferes with the translocation of the receptor to the nucleus.<sup>8</sup> SNARE-1 appears to be highly selective for prostate tumor cells. EPI-001 is the first molecule designed to bind to the AR N-terminal transactivation domain, which interferes with the protein-protein interactions, thus suppressing the AR interactions with regulatory domains.<sup>8</sup> This agent demonstrated clinical activity in androgen-dependent and -independent prostatic tumors in vivo. VN-124 is an analog of abiraterone acetate, (3-hydroxy-17-[1H-benzimidazole-

1-yl] androsta-5,16-diene), which has CYP17 activity but may increase AR turnover. Further clinical testing is needed to establish the clinical benefit of all these compounds.<sup>8</sup> A common theme regarding the new AR-targeting agents is that patients eventually relapse; this suggests that alternative tumor survival pathways evolve with treatment.

In CRPC treatment, the research has advanced significantly over the past several years. In addition to the agents modifying the AR activity, cytotoxic therapies, such as docetaxel and carbazitaxel, and immunotherapies (sipuleucel-T), have improved patients' survival.<sup>9,10</sup> The current clinical challenge is to understand better how to select patients for the appropriate therapy at the correct time. Identifying biomarkers that will predict outcomes of these novel treatments remains a high priority. Early trials with abiraterone acetate linked serum androgen and estradiol levels with PSA declines; however, we await further data in randomized trials to see if these bring a clinical benefit. Evolving data suggest that the AR is under stringent control of the retinoblastoma (RB) gene, a tumor suppressor that is functionally inactive in approximately 60% of CRPC patients.<sup>8</sup> RB-deficient tumors are resistant to androgen-deprivation therapy and might be more sensitive to DNA-damaging agents. These findings would suggest that tumors lacking RB function could be candidates for chemotherapeutic- rather than AR-blocking agents. Further studies are ongoing to test this hypothesis, but new biomarkers such as these are essential if we are going to improve outcomes in CRPC patients. ■

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