Castration-resistant prostate cancer (CRPC) is the second leading cause of cancer-related deaths in U.S. men, with approximately 30,000 deaths per year [1]. While metastatic CRPC remains an incurable disease, significant progress has been made in developing new therapeutics that prolong life. Targeting the androgen axis as well as the immune system has proven to improve outcomes. This article will discuss therapeutics that have demonstrated clinical benefits.

**Androgens/Androgen Receptor Signaling**

Studies have shown that intratumoral androgen levels remain high and androgen receptor activation persists in CRPC despite low levels of circulating androgens [2]. Montgomery et al [3] found that testosterone levels within metastases from anorchid men were significantly higher than levels within primary prostate cancers from eugonadal men. Other mechanisms of maintaining androgen receptor signaling in a low androgen environment (castration) include androgen receptor mutations [4], androgen receptor over-expression [5,6], androgen receptor splice variants [7], and changes in androgen receptor coregulatory proteins [8].

New therapies for prostate cancer with varied actions, including hormonal, targeted, immune, and cytotoxic, are rapidly emerging. For hormonal therapy, recent evidence suggests that continued targeting of androgen-dependent pathways is effective in CRPC even after treatment with chemotherapy. Clinical data now available for a C (17–20) lyase inhibitor (abiraterone) and an androgen receptor antagonist (MDV3100) show that both demonstrate favorable responses and, in the case of abiraterone, a survival advantage in CRPC following chemotherapy.

**CASE STUDY**

**Initial Presentation**

A 63-year-old man presents with an elevated prostate-specific antigen level (PSA) of 6.5 ng/mL. An ultrasound-guided prostate biopsy reveals high volume Gleason 4+3 = 7 adenocarcinoma of the prostate. Digital rectal examination was consistent with T1c clinical staging. A staging bone and CT scans did not show evidence of metastatic disease. Patient went on to be treated with combined modality external beam radiation and androgen deprivation therapy. PSA nadir was 0.08 ng/mL after 1 ½ years. The PSA trend over the ensuing period showed rising PSA with a doubling time of 10 months consistent with biochemical failure. Restaging scans did not show radiographic evidence of metastases. Patient was restarted on androgen deprivation therapy (ADT) and maintained on a luteinizing hormone-releasing hormone (LHRH) agonist when PSA...
reached 5 ng/mL. Subsequent PSA nadir was less than 0.1 ng/mL. The patient was maintained on a schedule of intermittent ADT. However, he subsequently had evidence of progressively rising PSA while on ADT despite confirmed castrate-level testosterone. The patient presents to discuss options for intervention.

**What are options for second-line hormonal therapy?**

A number of options are available for secondary hormone manipulation following failure of initial ADT for advanced disease. However, a survival benefit has not been demonstrated in a phase III trial. Included among the available options are administration of antiandrogens, withdrawal of antiandrogens, estrogens, P450 enzyme inhibitors, and 5-alpha reductase inhibitors.

**Antiandrogens**

The nonsteroidal or “pure” antiandrogens comprise those agents most commonly used in clinical practice. The nonsteroidal antiandrogens, namely, flutamide, bicalutamide, and nilutamide, block binding of dihydrotestosterone to the androgen receptor. The rationale for switching to another antiandrogen in patients who have progressed on an antiandrogen or complete androgen blockade is based upon the assumption that the specific antiandrogens interact differently with the androgen receptor. The potential utility of using an alternative nonsteroidal antiandrogen was illustrated by a retrospective series of 232 patients who progressed after initial treatment with complete androgen blockade [9]. Patients were observed for an antiandrogen withdrawal response before starting on an alternative antiandrogen. With the starting of an alternative antiandrogen, a PSA decrease of ≥ 50% was observed in 36% of patients and a lesser PSA decrease (< 50%) was seen in another 25%. There was no significant difference in those who switched from bicalutamide to flutamide compared with those who changed from flutamide to bicalutamide. Multivariate analysis found that any response to second-line antiandrogen therapy was significantly associated with an improved cause-specific survival.

**Flutamide**

Flutamide was the first “pure” antiandrogen. Flutamide has a half-life of 5 hours and is almost completely excreted in the urine. Its primary toxicities are common to the antiandrogen class of medications and include gynecomastia or breast tenderness in one-half of treated patients, liver dysfunction (fatal in rare cases), nausea, and diarrhea. The standard dose is 250 mg orally three times per day. The activity of flutamide was illustrated by a series of 209 men treated after failing initial hormonal therapy with either orchiectomy, diethylstilbestrol, or a LHRH agonist [10]. The overall response rate was 35%, and the mean duration of response was 24 months. Other smaller studies have yielded similar results.

No trial has established the superiority of flutamide compared to other forms of hormone therapy for second-line treatment of metastatic prostate cancer. One trial sponsored by the EORTC randomly assigned 201 men who were progressing after initial androgen ablation therapy to either flutamide (250 mg three times daily) or prednisone (5 mg four times daily) [11]. There were no significant differences between the groups in time to progression, overall survival, subjective response rate, biochemical response rate, or duration of response. However, patients receiving prednisone had less pain, fatigue, anorexia, gastrointestinal distress, and a better quality of life.

**Bicalutamide**

Several clinical studies have evaluated the use of high-dose bicalutamide as monotherapy in men with CRPC. In one study of 51 such men receiving bicalutamide (200 mg per day), PSA declines of 50% or greater were documented in 12 (24%) [12]. Similar results were noted in 2 other series using high-dose bicalutamide (150 mg per day) in men with CRPC progressing after initial treatment [13,14]. Differences between bicalutamide and flutamide may account for the responses observed in some patients who progressed while on treatment with flutamide. Bicalutamide has a significantly increased affinity for the androgen receptor. Furthermore, bicalutamide retains its antagonistic properties for the mutated or supersensitive androgen receptor [15]. In men treated with flutamide as part of a complete androgen blockade regimen, flutamide may exert selection pressure for androgen receptor mutations, thereby enhancing the subsequent inhibitory effect of bicalutamide [16].

**Nilutamide**

Nilutamide has a half-life of 56 hours. In addition to the side effects caused by its antiandrogenic properties, toxicities include delayed adaptation to darkness in 25% of patients,
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necia in 10%, reversible increases in hepatic transaminases in up to 8%, and alcohol intolerance in 5%. There are rare reports of interstitial lung disease caused by nilutamide.

Biochemical responses to nilutamide have been observed after both flutamide and bicalutamide failure [17]. In the largest series, 8 of 28 men treated with nilutamide who had failed prior flutamide or bicalutamide had a PSA response for longer than 3 months with nilutamide (200–300 mg daily). Men with a prior antiandrogen withdrawal response were significantly more likely to have a response to nilutamide than those without such a response.

A discussion of newer agents in this class follows later below.

Estrogens

The potential role of diethylstilbestrol (DES) (1 mg daily) as a second-line agent was evaluated in a trial in which 58 men who had progressed on LHRHa therapy were randomly assigned to either DES or bicalutamide [18]. Both the PSA response rate and median response durations were similar in the 2 groups (23% vs. 31% and 9 months vs. 12 months, respectively). Bicalutamide was better tolerated. Despite the prophylactic use of 75 mg of aspirin daily in the DES group, 3 of 7 patients with adverse effects had cardiovascular toxicity (congestive heart failure, pulmonary embolism, and stroke). Although active, the use of DES has largely been abandoned because of the cardiovascular side effects of estrogens and the availability of LHRH agonists. In the United States, DES is only available through specialty compounding pharmacies.

CYP 17 Lyase Inhibitors

The cytochrome P450 enzyme inhibitors block the synthesis of androgens in the adrenal gland, typically through inhibition of the enzyme 17,20-lyase. Ketoconazole, an imidazole antifungal agent that inhibits adrenal androgen synthesis and has a direct cytotoxic effect on prostatic cancer cells in vitro, is the prototypical drug in this class of agents. The usual dose of ketoconazole is 200 to 400 mg three times per day. It requires a low gastric pH for maximum absorption and thus is instructed to be taken on an empty stomach. In addition, antacids, proton pump inhibitors, and histamine H2-receptor antagonists should be avoided if possible. Adverse effects include nausea and vomiting in up to one-half of patients, skin rash in 10%, fatigue, nail dystrophy, asthenia, and gynecomastia. Moreover, high doses of ketoconazole can cause adrenal insufficiency by inhibition of other adrenal enzymes. Thus, ketoconazole is usually administered with concurrent hydrocortisone, which may complicate the interpretation of therapeutic results of ketoconazole in CRPC. Glucocorticoids reduce the pituitary production of adrenocorticotropic hormone (ACTH), resulting in suppression of adrenal steroidogenesis including adrenal androgens. Other possible mechanisms of glucocorticoid action include direct inhibition of tumor growth by disruption of intracellular signaling pathways and/or suppression of tumor lymphangiogenesis.

Using ketoconazole in conjunction with withdrawal of an antiandrogen as opposed to starting it after an adequate opportunity for an antiandrogen withdrawal response was the subject of phase III trial conducted by the Cancer and Leukemia Group B (CALGB 9583) [19]. In this trial, 260 patients who had progressed on ADT were randomly assigned to antiandrogen withdrawal plus simultaneous ketoconazole or antiandrogen withdrawal alone, with ketoconazole reserved for subsequent use upon progression [19]. There was no statistically significant difference in the median survival with the 2 treatment strategies (15.3 and 16.7 months, respectively).

A phase II study evaluating responses to blocking multiple steps in androgen synthesis with inhibitors of CYP17A1 (ketoconazole) and type I and II 5-alpha reductases (dutasteride) looked at 57 men with CRPC who were continued on gonadal suppression and treated with KHAD—ketoconazole (400 mg three times daily), hydrocortisone (30 mg/AM, 10 mg/PM), and dutasteride (0.5 mg/day). PSA response rate (≥ 50% decline) was 56%; the median duration of response was 20 months. In patients with measurable disease, 6 of 20 (30%) responded by the Response Evaluation Criteria in Solid Tumors (RECIST). Median duration of treatment was 8 months; 9 patients remained on therapy with treatment durations censored at 13 to 32 months. Median time to progression was 14.5 months [20]. As such, the response proportion to KHAD was at least comparable with previous studies of ketoconazole alone, whereas time to progression was substantially longer.

A discussion of newer agents in this class will follow later below.

5-alpha Reductase Inhibitors

The 5-alpha reductase inhibitors block the intraprostatic conversion of testosterone to dihydrotestosterone, while
the nonsteroidal antiandrogen blocks the cytoplasmic DHT receptor. Since testosterone conversion is blocked selectively within the prostate, serum testosterone levels are maintained during treatment. As a result, most men retain their pretreatment libido, potency, muscle mass, and erythropoietic capacity. These observations provide the rationale for treatment with the combination of finasteride and flutamide.

Uncontrolled studies have suggested that the combination of finasteride plus flutamide may be useful in this setting [21]. In the largest of these, 101 men with a rising PSA after definitive local therapy were treated with finasteride (5 mg daily) and flutamide (250 mg three times daily) [21]. In a preliminary report at a median follow-up of 59 months, nearly all patients (97%) had a greater than 80% decline in serum PSA, and only 22 men had progressed within 5 years of enrollment. Toxicity was described as mild.

Longer follow-up of men receiving oral combination therapy is needed, and a randomized phase III trial in men with early progression following local therapy will be required to validate this approach. Bicalutamide is also used with a 5-alpha reductase inhibitor in this setting. However, published studies specifically in PSA-only recurrence are lacking.

Case Continued

The patient was treated with second-line hormonal therapies including high-dose ketoconazole and then nilutamide in sequence. Despite initial PSA responses to each of these therapies, the patient subsequently had evidence of rising PSA to 15 ng/mL. A restaging CT and bone scan were obtained and showed new evidence of metastatic disease to the bones. Clinically, the patient remained asymptomatic.

What are the patient’s treatment options now?

Newer Approaches to Hormonal Therapy

MDV3100

MDV3100 is a direct inhibitor of androgen receptor, binding the receptor irreversibly with substantially higher affinity compared to bicalutamide. It also impairs nuclear translocation of androgen receptor, DNA binding, and coactivator recruitment. Scher et al [22] reported the safety and efficacy of MDV3100 in 140 patients with metastatic CRPC, both preand post-docetaxel. Patients were treated in dose-escalation cohorts from 30 to 600 mg. Anti-tumor effects were seen at all doses, including decreases in serum PSA of 50% or more in 56% of patients, responses in soft tissue in 22%, stabilized bone disease in 56%, and conversion from unfavorable to favorable circulating tumor cell counts in 49%. The median time to radiologic progression was 47 weeks for the entire cohort. The most common grade 3–4 adverse event was dose-dependent fatigue in 11% of patients, which generally resolved after dose reduction. The recommended phase III dose was 160 mg daily.

A randomized, placebo-controlled, double-blind phase III trial known as AFFIRM evaluating MDV3100 in CRPC previously treated with docetaxel completed accrual in October 2010. The primary endpoint is overall survival and secondary endpoints include progression-free survival, safety, and tolerability. If the trial is positive, it will provide a well-tolerated antiandrogen as a valuable treatment option for late-stage CRPC patients. Additionally, a phase III trial evaluating MVD3100 in CRPC pre-chemotherapy is now underway.

Abiraterone

Abiraterone (Zytiga) is a potent and irreversible inhibitor of CYP (17,20) lyase, which is the enzyme required for 2 essential steps in androgen biosynthesis in the testes, adrenal glands, and prostate tissue. Abiraterone has been tested in CRPC patients based on the hypothesis that extragonadal androgen sources may sustain tumor growth despite a castrate environment [23].

Several phase I and phase II studies evaluated the antitumor activity and safety of abiraterone acetate, alone or in combination with prednisone, in chemotherapy-naive or docetaxel pretreated patients with CRPC [23–29]. In a phase I dose-escalation study of abiraterone acetate, Ryan et al [25] evaluated safety, pharmacokinetics, and effects on steroidogenesis and PSA in 33 men with chemotherapy-naive CPRC with (n = 19) or without prior ketoconazole therapy. About 55% of patients had PSA responses at week 12, including 47% of patients who had prior ketoconazole therapy. Substantial declines in serum androgens (testosterone < 1.0 ng/dL) were seen with all doses. No dose-limiting toxicities were observed and it was concluded that abiraterone was well tolerated and
demonstrated activity in CRPC, including in patients previously treated with ketoconazole.

A study in 47 post-docetaxel CRPC patients treated with abiraterone acetate 1000 mg daily continuously showed declines of more than 50% in serum PSA and circulating tumor cell counts in 51% and 63% of patients, respectively. Partial responses (by RECIST) were reported in 27% of patients with measurable disease [27]. Another phase II study evaluated the efficacy and safety of abiraterone acetate in combination with prednisone in 58 men with progressive metastatic CRPC who experienced treatment failure with docetaxel-based chemotherapy. About 36% of patients had ≥ 50% decline in PSA, including 45% of ketoconazole-naive and 26% of ketoconazole-pretreated patients [28]. Overall, the drug was well tolerated and no abiraterone-related grade 4 events were seen.

The phase III trial of abiraterone acetate in CRPC patients previously treated with docetaxel was presented at the European Society for Medical Oncology meeting in October 2010 [30]. A total of 797 patients were randomized to receive abiraterone 1000 mg orally, plus prednisone/prednisolone 5 mg twice daily. The remaining 398 patients were assigned to placebo and the same dose of steroids. Treatment with abiraterone acetate led to a 35% reduction in the risk of death (hazard ratio, 0.65 [95% confidence interval {CI}, 0.54–0.77]; P < 0.001) that translated into a 36% increase in median survival. The patients on abiraterone and steroids achieved a median of 14.8-month survival compared with 10.9 months for patients who received placebo and steroids. In addition to meeting the primary endpoint of overall survival, the time to disease progression was 10.2 months among those on abiraterone and 6.6 months for the placebo patients (P < 0.001). In April 2011, the FDA approved abiraterone acetate for use in combination with prednisone for the treatment of patients with metastatic CRPC who have received prior chemotherapy containing docetaxel. At present, a phase III trial has been conducted in which men with asymptomatic or minimally symptomatic CRPC were randomly assigned to abiraterone or placebo (NCT00887198). Patients who received prior chemotherapy or ketoconazole were excluded from this trial. This trial has completed enrollment and results are pending. The primary endpoints of this trial are overall and progression-free survival.

**TAK700**

TAK-700 is an oral selective inhibitor of the CYP (17,20) lyase. Data from 26 participants with metastatic CRPC from the phase I portion of a phase I/II clinical trial evaluating TAK-700 demonstrated that patients who received TAK-700 300 mg orally twice daily for 3 or more cycles experienced a PSA response [31]. Testosterone levels dropped to extremely low concentrations. There were no dose-limiting toxicities during the phase I portion of the trial. The phase II portion of this study is ongoing and will further examine the safety and efficacy of TAK-700 and the need for concomitant prednisone. Several phase III trials are ongoing, including an evaluation of TAK-700 in CRPC patients without metastases and in CRPC combined with docetaxel.

**TOK-001**

TOK-001 is an orally bioavailable small-molecule CYP (17,20) lyase inhibitor with additional direct AR antagonist activity. A phase I/II study of TOK-001 in CRPC, known as ARMOR1, is currently recruiting patients.

**Chemotherapy in CRPC**

There are 4 chemotherapeutic agents that are FDA-approved for CRPC: estramustine, mitoxantrone, docetaxel, and cabazitaxel [32–35]. Cabazitaxel is a tubulin-binding semisynthetic taxane that retained activity against docetaxel-resistant CRPC in preclinical models. Cabazitaxel in combination with prednisone was approved by the FDA in June 2010 for the treatment of patients with metastatic CRPC who had been previously treated with docetaxel.

In the randomized, open-label phase III TROPIC study, researchers compared the efficacy and safety of cabazitaxel plus prednisone to mitoxantrone plus prednisone in men with metastatic CRPC pretreated with docetaxel [35]. Participants received either 12 mg/m² mitoxantrone (n = 377) or 25 mg/m² cabazitaxel (n = 378) every 3 weeks; all patients received prednisone 5 mg twice daily. The median survival was 15.1 months (95% CI, 14.1–16.3) in the cabazitaxel group and 12.7 months (95% CI, 11.6–13.7) in the mitoxantrone group. The most common grade 3 or higher adverse event was neutropenia. Cabazitaxel is the first cytotoxic drug to improve survival in patients with metastatic CRPC previously treated with
docetaxel, providing a 30% reduction in the risk of death and an improved median overall survival compared with mitoxantrone. Upcoming phase III trials will compare cabazitaxel to docetaxel in the first-line chemotherapy setting and will compare 25 vs. 20 mg/m² of cabazitaxel post-docetaxel therapy.

As reported at the 2010 annual meeting of the American Society of Clinical Oncology, a phase III trial of docetaxel and bevacizumab (CALGB 90401), a humanized monoclonal antibody that recognizes all VEGF isoforms, showed that the addition of bevacizumab to docetaxel/prednisone in metastatic CRPC failed to provide a survival benefit [36]. Notably, while bevacizumab did not improve overall survival there is at least a suggestion of benefit in certain subgroups, and therefore further analysis of this study may shed light on patients who may benefit from this treatment.

**Ongoing Phase III Trials**

Agents targeting adrogen receptor activation and local steroidogenesis, angiogenesis, apoptosis, chaperone proteins, the insulinlike growth factor pathway, RANK ligand, endothelin receptors, and Src family kinases are entering, or have recently completed, accrual to phase III trials.

**Immunotherapy**

FDA approval of sipuleucel-T for CRPC has marked the first time an immunotherapy has improved median overall survival in solid tumors. Other approaches are attempting to extend and improve upon these results.

**Sipuleucel-T**

Sipuleucel-T (APC 8015, Provenge) is an autologous, dendritic cell-based vaccine that reduced the risk of death among men with metastatic CRPC and was approved by the FDA in April 2010. In the double-blind, placebo-controlled, phase III IMPACT study, 512 patients were randomly assigned in a 2:1 ratio to receive either sipuleucel-T (341 patients) or placebo (171 patients) administered intravenously every 2 weeks for a total of 3 infusions [37]. In the sipuleucel-T group, there was a relative reduction of 22% in the risk of death as compared with the placebo group. This reduction represented a 4.1-month improvement in median survival (25.8 months vs. 21.7 months in the placebo group). This study, together with earlier trials [38,39], provided the basis for the approval of sipuleucel-T by the FDA. Notably, the majority of men in the studies had chemotherapy-naive CRPC as opposed to those in the abiraterone and cabazitaxel phase III trials who had docetaxel-resistant disease. It is also worth noting that none of these men received concurrent steroids.

**Prostvac, Ipilimumab, and Others**

PROSTVAC-VF is a sequentially dosed combination of 2 different poxviruses which each encode PSA plus 3 immune-enhancing co-stimulatory molecules—intercellular adhesion molecule-1, B7-1, and leukocyte function-associated antigen 3 (TriCom) [40]. Results with 3-year follow-up of a randomized, double-blind phase II trial of PROSTVAC-VF vs. empty vector in 122 men with minimally symptomatic metastatic CRPC revealed an overall survival benefit in the PROSTVAC-VF arm (25.1 vs. 16.6 months for controls) [41]. A randomized phase III study using docetaxel with or without PROSTVAC-VF as first-line therapy for men with metastatic CRPC is planned.

Anticytotoxic T-lymphocyte antigen-4 (CTLA-4) therapies represent a novel approach to cancer treatment via disruption of immune tolerance to antigens located on tumor cells. Several trials using the anti-CTLA-4 antibody ipilimumab have been conducted in men with metastatic CRPC and showed PSA declines as well as radiological responses [42,43]. A multicenter randomized phase III study in metastatic, docetaxel-refractory patients is currently underway and aims to examine the combination of ipilimumab with focal radiation.

Another co-inhibitory receptor molecule expressed on activated T lymphocytes that functions as an immune checkpoint is programmed death-1 (PD-1) [44]. In many human tumors, expression of the PD-1 ligand correlates with a poorer prognosis. A phase I dose-escalation trial using MDX-1106 (a fully human anti-PD-1 monoclonal antibody) in 39 patients with refractory metastatic solid tumors (including 8 metastatic CRPC) was completed. MDX-1106 administered biweekly was well tolerated [45]. A phase Ib study of MDX-1106 in patients with selected refractory/relapsed malignancies is underway and the trial will enroll men with CRPC [46].

**In Early Development**

Multiple targeted agents are in active clinical development and a selected few will be reviewed.
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**XL184**
XL184 (cabozantinib) is a small molecule receptor tyrosine kinase (RTK) inhibitor that has a strong affinity for the hepatocyte growth factor receptor (MET), RET, and vascular endothelial growth factor receptor 2 (VEGFR2) [47]. In a phase II randomized discontinuation trial, 168 patients with measurable progressive metastatic prostate cancer received 12 weeks of lead-in treatment with XL184 [48]. After the initial treatment, patients with a partial or complete response were allowed to continue treatment in an open label extension. Those with stable disease were randomized to XL184 or placebo, with those who received placebo going back to XL184 upon progressive disease. Patients with progressive disease after the initial 12 weeks of treatment and those who progressed on XL184 following randomization came off protocol. Preliminary results were presented at the 2011 American Society of Clinical Oncology meeting. Patients included 47% with visceral metastases, 78% with bone metastases, and 47% docetaxel-pretreated. Although only 4% of patients met RECIST criteria for a partial response, 74% had evidence of tumor regression. Progression-free survival following randomization was significantly longer with XL184 compared with placebo (21 versus 6 weeks). Among the 108 patients with serial bone scans, 86% had complete or partial resolution of lesions on bone scan as early as week 6. Eight patients (12%) had stable disease (SD) and 1 patient (2%) had progressive disease. In 28 patients receiving narcotics for bone pain, 64% had improved pain and 46% decreased or halted narcotics, per investigator. Median maximum rise in hemoglobin in anemic patients (Hb < 11 g/dL) was 2.2 g/dL (range, 0.6–3.5). Observed osteoclast and osteoblast effects included 55% had declines of ≥ 50% in plasma C Telopeptide; 56% of patients with elevated tALP had declines of ≥ 50%. Objective tumor shrinkage occurred in 84% of patients. Objective response rate at week 12 was 5%; additional partial responses (PR) await confirmation. PSA changes were independent of clinical activity. Overall, week 12 disease control rate (PR+SD) was 71%. Randomization was halted and patients unblinded due to high rates of bone scan resolution and pain relief [48]. There is a planned phase 1 trial of XL184 plus abiraterone in metastatic CRPC patients.

**Poly (ADP-ribose) Polymerase**
Poly (ADP-ribose) polymerase (PARP) has strong affinity for DNA strand breaks and cycles on and off the DNA ends to allow DNA repair. A PARP inhibitor MK-4827 has recently been reported to show antitumor activity in patients with a range of solid tumors, including prostate cancer. A pilot study combining ABT-888 inhibitor with temozolomide in CRPC patients who have failed up to 2 nonhormonal systemic therapies was initiated in early 2010 and results are pending.

**Case Follow-up**
The patient, who was asymptomatic, went on to receive sipuleucel-T therapy for metastatic CRPC. He tolerated his therapy very well. However, his PSA continued to rise with subsequent development of symptoms of bone pains in the context of progressive disease on bone scan. Given new symptomatic disease, he went on to receive docetaxel chemotherapy every 3 weeks. He responded initially but then developed taxane-refractory disease as evidenced by rising PSA. Given fatigue and lower extremity edema as a direct result of docetaxel therapy, he was started on abiraterone with symptomatic improvement and good PSA response. Unfortunately, after 4 months of therapy he again began to develop bone pains in the context of rising PSA and disease progression on both CT and bone scans. In discussion of treatment options including standard therapy with cabazitaxel or therapy with XL-184 on clinical trial, he opted for enrollment in the clinical trial.

**CONCLUSION**
While metastatic CRPC remains an incurable disease, significant progress has been made in developing new therapeutics that prolong life. Currently, there are multiple approved treatment options for this setting including sipuleucel-T, docetaxel, and cabazitaxel, in addition to abiraterone (Table 1) [49]. Both cabazitaxel and abiraterone are approved specifically for use

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**Table 1. Drugs Approved for Treatment of CRPC**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitoxantrone/prednisone</td>
<td>First-line metastatic</td>
</tr>
<tr>
<td>Docetaxel/prednisone</td>
<td>First-line metastatic</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>Post-docetaxel metastatic</td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>Pre-docetaxel asymptomatic or minimally symptomatic metastatic (no visceral mets)</td>
</tr>
<tr>
<td>Abiraterone/prednisone</td>
<td>Post-docetaxel metastatic</td>
</tr>
</tbody>
</table>

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**References**

[47] [48] [49]
in patients who have had prior docetaxel chemotherapy. There are no clinical trials defining the optimal sequencing of these agents. Theoretically, treatment with abiraterone after docetaxel but before cabazitaxel may allow patients to avoid the toxicity associated with continuous exposure to taxane chemotherapy and possibly delay the emergence of taxane-resistant disease. Conversely, using cabazitaxel prior to abiraterone may prolong sensitivity to taxanes. Other patient-specific factors, including age and comorbidities, may also influence the choice of treatment. Novel agents in clinical trials are likely to further alter the treatment of CRPC (Table 2).

**Table 2. Phase III Trials in CRPC**

<table>
<thead>
<tr>
<th>Experimental</th>
<th>Mechanism of Action</th>
<th>Patients</th>
<th>Primary Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel/prednisone plus afiblercept</td>
<td>Soluble VEGF fusion protein comprised of extracellular domains of VEGF receptors 1 and 2 fused to IgG. Binds to and neutralizes VEGF.</td>
<td>First-line metastatic</td>
<td>OS</td>
</tr>
<tr>
<td>Docetaxel/prednisone plus lenalidomide</td>
<td>Immunomodulatory and anti-angiogenic</td>
<td>First-line metastatic</td>
<td>OS</td>
</tr>
<tr>
<td>Docetaxel/prednisone plus atrasentan</td>
<td>Endothelin receptor antagonist</td>
<td>First-line metastatic</td>
<td>OS, PFS</td>
</tr>
<tr>
<td>Docetaxel/prednisone plus zibotentan</td>
<td>Endothelin receptor antagonist</td>
<td>First-line metastatic</td>
<td>OS</td>
</tr>
<tr>
<td>Docetaxel/prednisone plus dasatinib</td>
<td>SRC kinase inhibitor (targets stromal–epithelial interactions)</td>
<td>First-line metastatic</td>
<td>OS</td>
</tr>
<tr>
<td>Docetaxel/prednisone plus OGX-11</td>
<td>Antisense oligonucleotide that inhibits clusterin (cell survival protein)</td>
<td>First-line metastatic</td>
<td>OS</td>
</tr>
<tr>
<td>Tasquinimod</td>
<td>Anti-angiogenic</td>
<td>Chemotherapy-naive, asymptomatic or minimally symptomatic metastatic</td>
<td>PFS</td>
</tr>
<tr>
<td>Abiraterone acetate/prednisone</td>
<td>CYP17 inhibitor (inhibits androgen biosynthesis)</td>
<td>Chemotherapy-naive, asymptomatic or minimally symptomatic metastatic</td>
<td>OS, PFS</td>
</tr>
<tr>
<td>MDV3100</td>
<td>Inhibits androgen receptor binding, translocation to nucleus, and DNA binding</td>
<td>Post-docetaxel metastatic</td>
<td>OS</td>
</tr>
<tr>
<td>TAK-700/prednisone</td>
<td>Inhibits 17,20 lyase (androgen biosynthesis)</td>
<td>Chemotherapy-naive, metastatic</td>
<td>OS, PFS</td>
</tr>
<tr>
<td>PROSTVAC +/- GM-CSF</td>
<td>Recombinant vaccinia viral cassette that expresses PSA gene and costimulatory molecules, followed by fowlpox booster</td>
<td>Asymptomatic or minimally symptomatic chemotherapy-naive metastatic</td>
<td>OS</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Human monoclonal antibody that blocks CTLA-4 (T cell receptor)</td>
<td>Asymptomatic or minimally symptomatic chemotherapy-naive metastatic</td>
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<tr>
<td>Ipilimumab</td>
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<td>Post-docetaxel metastatic</td>
<td>OS</td>
</tr>
</tbody>
</table>

OS = overall survival; PFS = progression-free survival.

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