Castration-resistant prostate cancer is a disease that is fatal in virtually all patients. Docetaxel chemotherapy became the standard front-line agent based on the results of the TAX327 trial in 2004, with a survival advantage of 3 months achieved over mitoxantrone. Over the past few years, an improved understanding of the molecular biology of castration-resistance has resulted in expansion of the treatment armamentarium for advanced prostate cancer with the emergence of novel: androgen receptor-directed therapies, cytotoxic chemotherapies, as well as immunotherapies. Four different agents have very recently gained approval by the US FDA for the treatment of castration-resistant prostate cancer and this review will summarize the development, mechanism of action and safety and efficacy of these agents as demonstrated in preclinical, as well as clinical studies.

Keywords: abiraterone • cabazitaxel • castration-resistant prostate cancer • denosumab • ipilimumab • MDV3100 • sipuleucel-T

Androgen deprivation therapy is the most effective systemic treatment for recurrent prostate cancer; however, the vast majority of patients will eventually develop resistance to hormonal approaches necessitating other forms of therapy. Although several chemotherapeutic strategies have been employed to treat castration-resistant prostate cancer (CRPC), it was not until 2004 that one such approach was shown to be life-prolonging. In that year, two Phase III clinical trials reported a survival advantage with the use of docetaxel chemotherapy in men with metastatic CRPC, resulting in the US FDA-approval of this agent. However, while docetaxel is both palliative and life-prolonging, it is not the ultimate answer for patients with CRPC, as virtually all men develop eventual resistance to this chemotherapy agent or are unable to tolerate its toxicities long term.

Until 2010, there were no additional treatment options conferring a survival benefit for patients with CRPC, although mitoxantrone was often employed for its palliative effects on bone pain. This situation changed in 2010 when an autologous immunotherapy product, sipuleucel-T, was FDA-approved for the treatment of minimally symptomatic or asymptomatic metastatic CRPC, based on the results of a randomized Phase III trial comparing this agent against a placebo. In that same year, a randomized Phase III trial demonstrated a survival advantage for a novel taxane, cabazitaxel, over mitoxantrone in men with metastatic CRPC that had progressed after prior docetaxel therapy. Based on those results, cabazitaxel was approved by the FDA for the second-line treatment of metastatic CRPC. Several months later, an oral agent with the ability to suppress nongonadal androgen synthesis, abiraterone, was also reported to improve survival in a Phase III study when evaluated against placebo in men with docetaxel-pretreated metastatic CRPC, resulting in the FDA approval of this agent for patients that had previously received docetaxel.

In addition to these life-prolonging therapies, novel bone-targeting approaches are also being developed to address skeletal complications resulting from bone metastases. To this end, an osteoclast-inhibiting agent, denosumab, was FDA-approved in 2010.
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for the prevention of skeletal-related events (SRE) in men with castration-resistant bone metastases after showing superiority against the previously approved bisphosphonate zoledronic acid. Given this abundance of new treatment options, a new question emerges: How do we select men for each new therapy, and in what sequence should these agents rationally be given? This review discusses the four novel therapies that have recently become available for the management of patients with CRPC, and will also highlight select emerging agents that have shown promising activity and are currently in Phase III clinical development.

Androgen-receptor axis targeted therapy

Androgen deprivation therapy is the mainstay of treatment in patients with advanced prostate cancer with initial response rates of 80–90%. Despite such high success rates in this patient population, virtually all patients eventually go on to develop resistance to androgen ablative therapy. Many of these patients will then receive systemic cytotoxic chemotherapy. Nevertheless, the androgen receptor (AR) axis continues to play an important role in the progression of castration-resistant prostate cancer via mechanisms that include:

- Non-gonadal (e.g., adrenal) androgen synthesis and secretion;
- Intratumoral androgen synthesis;
- Increase in AR expression in response to castrate levels of androgen;
- AR amplification and mutation;
- Ligand-independent or constitutive AR activity [1–6].

This past year has seen significant advances in the development of potent inhibitors of the AR axis, which have shown clinical efficacy in patients with CRPC treated with other second-line hormonal agents and docetaxel chemotherapy. Two of the agents that are furthest in development are abiraterone acetate: a cytochrome P (CYP) 17,20 lyase inhibitor (Figure 1), which was recently approved for patients postdocetaxel, and MDV3100: a direct AR antagonist that has completed Phase III enrolment in the same population.

Abiraterone acetate

It is a well-established fact that the non-gonadal (e.g., adrenal) source of androgen production contribute significantly to total circulating testosterone and accounts for up to 10% of baseline testosterone in castrated men. As such, castration-resistant disease still remains a hormonally driven disease by, in part, adrenal gland production of dehydroepiandrosterone and androstenedione that are converted peripherally to testosterone. Initial evidence for the effectiveness of lowering adrenal androgen production on CRPC was provided by studies performed by Charles Huggins who demonstrated that approximately 20% of patients with CRPC would have a secondary clinical response to adrenalectomy [7]. On this basis, non-specific inhibitors of adrenal hormonal synthesis, such as ketoconazole, which can rapidly lower circulating testosterone to undetectable levels, have provided benefit in patients with castration-resistant disease with reported prostate-specific antigen (PSA) response rates of 20–60% [8,9]. A recent Phase II trial of ketoconazole combined with dutasteride in 57 men with asymptomatic CRPC demonstrated a 56% PSA response rate and a 30% objective response rate with a median time to PSA progression of 14.5 months (Figure 2) [10]. While this response rate is similar to those observed in Phase II and III trials of abiraterone acetate and MDV3100, no properly powered randomized study with a survival end point has ever been performed with ketoconazole in men with CRPC. In addition, the drug has considerable toxicity in a subset of men. Responses are also transient, lasting on average between 4 and 6 months.

Abiraterone acetate is an oral, selective and irreversible small molecule inhibitor of CYP17, a rate-limiting enzyme in testosterone biosynthesis located in the testicular Leydig cells and in cells of the adrenal cortex (Figure 1). Preclinical studies showed significant reduction in androgenic steroid production downstream from CYP17 and resulted in decreased prostate, testicular and seminal vesicle weights. In a Phase I

Figure 1. Abiraterone and its effect on androgen biosynthesis. ACTH: Adrenocorticotropic hormone; DHEA: Dehydroepiandrosterone.
The unfolding treatment landscape for men with castration-resistant prostate cancer

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Figure 2. Summary of results from trials of abiraterone acetate [11,13,14], MDV3100 [19], AAWD plus ketoconazole [8] and KHAD [10] in terms of PSA responses (≥50% decreases in PSA), objective responses, and time to PSA progression (≥25% increase in PSA from baseline/nadir). AAWD: Antiandrogen withdrawal; KHAD: Ketoconazole plus dutasteride; PSA: Prostate-specific antigen.

The study, 21 patients with castration-resistant disease after multiple hormonal therapies were treated with escalating once-daily doses of abiraterone from 250 to 2000 mg daily [11]. Antitumor activity was observed at all doses. Anticipated toxicities were attributable to secondary mineralocorticoid excess, hypertension, hypokalemia and lower-limb edema which were easily manageable with a mineralocorticoid receptor antagonist. There were no grade 3 or 4 toxicities in all doses. PSA reductions of >30, >50 and >90% were observed in 14 (66%), 12 (57%) and 6 (29%) patients and lasted between 69 and 578 days [4]. The dose selected for Phase II investigations was 1000 mg/day when it was observed that corticosterone and deoxycorticosterone levels reached plateau levels at abiraterone doses greater than 750 mg.

Another Phase I/II study involving patients in prechemotherapy setting [12], PSA declines were observed at all dose levels studied in the Phase I portion: 52% of patients achieved >50% decline in PSA compared with baseline values which lasted between 69 and >578 day. Five out of eight (62%) patients with measurable disease had RECIST-defined confirmed partial response. In the second study, 18 of 33 (55%) patients in the Phase I cohort experienced a decline in PSA by >50% and in 9 of 24 patients (37.5%) with measurable disease showed partial response per RECIST. The Phase II portion of the study included 42 patients treated with a daily dose of 1000 mg, which showed median time to PSA progression (TTPP) on abiraterone acetate for all Phase II patients was 225 days (95% CI: 162–287 days). Of note, patients with prior exposure and progression on ketoconazole also experienced a PSA decline on abiraterone. Furthermore, a separate Phase II study evaluated abiraterone in 47 patients who were treated with docetaxel chemotherapy. This study demonstrated PSA declines of >30, >50 and >90% in 68, 51 and 15% of patients, respectively. Partial responses (by RECIST) were reported in eight (27%) patients. Median time to PSA progression was 169 days. Furthermore, 11 of 27 patients (41%) had a decline from at least 5 to less than 5 CTCs, and 18 (67%) out of 27 had a >30% decline in CTCs after starting treatment with abiraterone acetate [12].

Based on the promising results of the above studies, two large randomized placebo-controlled Phase III trials were launched, one in pre- and the other in postdocetaxel settings, both with the primary end point of overall survival. Most recently reported are the results of the Phase III study evaluating abiraterone in docetaxel-pretreated patients [13]. This study was the first to evaluate the effect of a second-line hormonal agent on survival in men with CRPC. Since no survival data existed for other second-line hormonal agents in CRPC, this Phase III study (COU–AA–301) compared the effects of abiraterone acetate plus prednisone to placebo plus prednisone. The study enrolled 1195 patients in a 2:1 ratio to 5 mg of prednisone twice-daily with either abiraterone acetate 1000 mg (797 patients) or placebo (398 patients). After a median follow up of 12.8 months, overall survival was longer in the abiraterone acetate-prednisone group than in the placebo-prednisone group (14.8 vs 10.9 months; HR: 0.65; 95% CI: 0.54–0.77; p < 0.001). Data were unblended at the determined interim analysis since these results exceeded the criteria for the interim analysis. Secondary end points, including time to PSA progression (10.2 vs 6.6 months; p < 0.001), progression-free survival (5.6 vs 3.6 months; p < 0.001), and PSA response rate (29 vs 6%; p < 0.001), favored the treatment group. The safety profile was as expected from earlier studies, which were largely due to mineralocorticoid excess hypokalemia, hypertension and fluid retention, which were predominantly grade 1 or 2 and easily controlled by the use of low-dose prednisone or prednisolone. On the basis of these results, abiraterone acetate was approved by the FDA for the relatively restricted indication of CRPC patients after failing docetaxel. However, some investigators have argued that abiraterone will probably be effective in all patients with CRPC, even those who have not yet received prior chemotherapy [14]. To this end, accrual is complete for the placebo-controlled Phase III trial in the prechemotherapy setting (COU–AA–302) and the survival results are awaited. Additional androgen biosynthesis inhibitors in clinical development include orteronel (TAK–700) as well as TOK–001, and these are reviewed elsewhere [15].
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■ MDV3100
The data from the abiraterone acetate studies suggest that some proportion of CRPC cells remain hormonally sensitive through the alteration of the AR axis via mechanisms outlined above. In preclinical studies, AR overexpression has been shown to be sufficient to drive the development of both castration-resistant and anti-androgen-resistant disease [16]. MDV3100 is a second-generation non-steroidal antiandrogen that binds to the AR with higher affinity than nilutamide or bicalutamide [17]. Furthermore, unlike nilutamide and bicalutamide, MDV3100 does not exhibit agonistic activity in the setting of AR overexpression. Such agonistic activity can result in aberrant recruitment of coactivators which lead to target gene activation rather than repression. In this regard, MDV3100 suppressed growth and induced apoptosis in a human prostate cancer cell line (VCaP) that was selected to be resistant to bicalutamide [18].

Based on these preclinical studies, a Phase I/II trial was performed in men with CRPC [17]. The majority of patients in this study had metastatic disease (95%): all patients had received at least one line of hormonal therapy and 75 (54%) patients had previously received systemic chemotherapy. Antitumor effects were seen at all doses with decreases in serum PSA of 50% or more in 78 (56%) patients, responses in soft tissue in 13 (22%) of 59 patients, and stabilized bone disease in 61 (56%) of 109 patients. The median time to radiological progression was 47 weeks (95% CI: 34–not reached). Most interestingly, MDV3100 resulted in >50% PSA decline in over half of these patients (51%) in a subset analysis involving postchemotherapy patients. The most common adverse event was fatigue, with frequent dose reductions needed at doses of 240 mg and above. Two incidences of witnessed seizures were documented in patients receiving 360 mg per day and above. Only one of the 87 patients treated with the dose of 240 mg or less discontinued treatment for an adverse event. AR binding appeared to be saturated at plasma concentrations of 5–15 µg/ml, which was achieved consistently in patients at 150 mg per day dose. Based on these combined results, the recommended dose for Phase III studies was 160 mg per day. Results are awaited on a multicenter randomized, placebo-controlled, double-blind Phase III trial with the primary end point of overall survival evaluating MDV3100 versus placebo in men with CRPC who were postdocetaxel chemotherapy (AFFIRM) that completed accrual in October of 2010. An additional placebo-controlled, randomized multicenter Phase III study evaluating MDV3100 in the prechemotherapy setting is currently undergoing accrual (PREVAIL). Other novel AR-directed agents in early clinical development include ARN-509 (a potent irreversible inhibitor of AR), EZN-4176 (an AR mRNA inhibitor), and AZD-3514 (a downregulator of AR) [15].

Chemotherapy for CRPC
With the results of TAX327 trial demonstrating a survival benefit with docetaxel plus prednisone over mitoxantrone plus prednisone, the regimen of every 3 week treatment with docetaxel plus prednisone became the standard first-line therapy in CRPC patients [19]. After the success of the TAX327 trial, several combination chemotherapy regimens have been tested in an attempt to improve upon the docetaxel backbone; including estramustine, vinorelbine, capcitabine, epirubicin and carboplatin [20–23]. These combinations did not show benefit over single-agent docetaxel therapy. In addition to these combination studies, other single chemotherapy agents have been evaluated for potential effect on CRPC in patients who are docetaxel refractory and whose disease is unfortunately almost always fatal within 1–2 years. This approach led to the development of cabazitaxel, a novel taxane which has shown a survival benefit over mitoxantrone in Phase III studies leading to its FDA approval in the past year for the treatment of patients who have progressed after docetaxel chemotherapy [24].

■ Cabazitaxel
Cabazitaxel is a semi-synthetic taxane derivative of docetaxel with an additional methyl group that confers two advantages over docetaxel: first, the presence of an additional methyl group eliminates the P-glycoprotein (P-gp) affinity resulting in the potential for enhanced antitumor activity in prostate cancer cells that may become docetaxel-refractory due to enhanced efflux of drug via P-gp pumps [24]. A second advantage of cabazitaxel is its ability to penetrate the blood–brain barrier, which may have clinical relevance in other cancer types with a higher predilection for brain metastases compared with prostate cancer. Indeed, cabazitaxel showed antitumor activity in vitro, not only in docetaxel-sensitive cell lines but also in docetaxel and paclitaxel-resistant models. In its clinical development [25], 25 patients with advanced solid tumors were enrolled in a Phase I study evaluating doses that ranged from 10 mg/m² to 25 mg/m² in 5 mg/m² increments. The most prominent adverse event was neutropenia, with one patient experiencing grade-4 neutropenia and another patient experiencing febrile neutropenia, both at the 25 mg/m² dose. There was no grade-3 or -4 neurotoxicities. Most common non-hematologic toxicities were diarrhea (56%) nausea, vomiting, neurotoxicity and fatigue, which were mild to moderate and easily manageable. Only one patient experienced grade-3 diarrhea. Two partial responses were observed, both of which were in patients with metastatic
patients received 20 mg/m² of cabazitaxel every 3 weeks. In this Phase II study, metastatic breast cancer patients. In this Phase III study of cabazitaxel in metastatic CRPC patients. In this Phase II study, metastatic breast cancer patients received 20 mg/m² of cabazitaxel every 3 weeks. Patients received a median of four cycles (1–25) and after the first cycle, 20 patients who experienced no toxicities had dose escalation to 25 mg/m². This study showed a response rate of 14%, including eight partial and two complete responses. A total of 18 patients experienced stable disease for at least 3 months. Overall survival was 12.3 months with median time to progression of 2.7 months. As anticipated, neutropenia was the most common adverse event (73%), followed by leucopenia (55%), fatigue (35%), nausea (32%) diarrhea (30%), vomiting (18%), neuropathy (17%) and hypersensitivity reaction (6%).

A multicenter, randomized, Phase III study (TROPIC) evaluating cabazitaxel conducted in 775 patients with metastatic CRPC, who had progressed during or after docetaxel chemotherapy, was recently reported [26]. Patients were randomized equally into two groups: cabazitaxel 25 mg/m² versus mitoxantrone 12 mg/m², both given every 3 weeks for a maximum of ten cycles. Both groups also received prednisone 5 mg twice-daily. The trial’s primary end point was overall survival and secondary end points included progression-free survival, PSA response, PSA progression, response rate measured per RECIST pain response, and time to radiographic progression. This study showed a statistically significant overall survival benefit in patients treated with cabazitaxel with median survival of 15.1 months (95% CI: 14.1–16.3) in the cabazitaxel group versus 12.7 months (95% CI: 11.6–13.7) in the mitoxantrone group. Risk of death was reduced by 30% with cabazitaxel compared with mitoxantrone (HR: 0.7; 95% CI: 0.59–0.83; p < 0.0001). Median progression-free survival was 2.8 months (95% CI: 2.4–3.0) in the cabazitaxel group and 1.4 months (95% CI: 1.4–1.7) in the mitoxantrone group (HR: 0.74, 95% CI: 0.64–0.86; p < 0.0001). Additional secondary end points including PSA response, as well as tumor response, met statistically significant improvements in the cabazitaxel arm compared with the mitoxantrone arm. The median number of cycles of drug administered was six for cabazitaxel and four for mitoxantrone. Side effects were significantly more pronounced in the cabazitaxel group compared with the mitoxantrone-treated group, with 82% of patients experiencing grade 3 or greater neutropenia, leading to 8% of patients having neutropenic fever. Treatment-related deaths were more frequent in the cabazitaxel group (18 [4.9%] vs 9 [2.4%]) than in the mitoxantrone group. Further studies to find optimal dosing for maximal therapeutic index, as well as its efficacy in the predocetaxel setting, are critical questions to be addressed at this time. However, based on this trial, cabazitaxel was approved in the USA for the treatment of patients with progressive disease during or after docetaxel chemotherapy. Table 1 highlights some key patient characteristics and efficacy results from the two pivotal studies evaluating second-line therapies in men with docetaxel-refractory CRPC. Although across-trial comparisons should be interpreted with caution, this table shows that overall survival times in the two trials were similar while other efficacy end points differed between the two studies (Table 1).

Other chemotherapeutic agents
As stated previously, many chemotherapeutic agents have been added to docetaxel in an attempt to improve upon the docetaxel backbone without clear success. Moreover, newer agents are also under study in the setting of castration resistance, although clear benefit has not been established thus far. As an example, satraplatin is an orally active platinum agent which has exhibited activity in cisplatin-resistant preclinical tumor models, including prostate cancer patients in early clinical studies. Satraplatin was evaluated in a Phase III, placebo-controlled, randomized trial in 950 docetaxel-resistant prostate cancer patients [27]. Progression-free survival was significantly increased in the treatment arm (1 year progression-free survival rate of 17 vs 7%, median progression-free survival 11.1 vs 9.7 weeks, HR: 0.67; 95% CI: 0.57–0.77). However, there was no difference in overall survival in the treatment arm (61 weeks for both arms, HR: 0.98; 95% CI: 0.84–1.15). Another agent extensively studied is ixabepilone, a non-taxane tubulin polymerizing epothilone agent which showed activity in early clinical studies in CRPC. A Phase II study conducted by the SWOG included 41 men with CRPC in prechemotherapy setting that showed 33% PSA responses and 25% response rate [28]. Median survival was 18 months. In another study, 82 men in a post-taxane setting were randomized to ixabepilone or mitoxantrone plus prednisone. PSA response rates were similar with the two regimens. Ixabepilone has also been studied in randomized trials with or without estramustine, but median time to tumor progression was similar in both arms [29]. However, further clinical development of ixabepilone in CRPC is not planned.
Cancer immunotherapy refers generally to approaches that attempt to treat cancer by activating immune responses against malignant cells while overcoming tumor-induced tolerance \[30\]. Although not traditionally considered a disease amenable to immune-directed therapies, prostate cancer may in fact be an ideal target for immunologic attack \[31\] because it is a slow-growing disease (allowing a stimulated immune system time to generate an antitumor response) and produces several tissue-specific proteins that may serve as tumor antigens: these include PSA and prostatic acid phosphatase (PAP). The notion of prostate/prostate cancer-specific antigens has been applied to the development of sipuleucel-T, an autologous PAP-loaded antigen-presenting cell immunotherapy \[32\]. During the course of treatment with sipuleucel-T, a patient’s own antigen-presenting cells are collected by leukapheresis and co-incubated \textit{ex vivo} with a fusion protein containing PAP linked to granulocyte macrophage colony-stimulating factor (GM-CSF). After culturing this fusion protein with the antigen-presenting cells, the primed immunotherapy product is then reinfused back into the patient, activating T cells via MHC class I and class II molecules and resulting in a PAP-directed antitumor lytic response \[33\].

Table 1. Comparison of the two pivotal second-line trials for men with metastatic castration-resistant prostate cancer: COU-AA-301 versus TROPIC.

<table>
<thead>
<tr>
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<th>Cabazitaxel/prednisone (TROPIC)</th>
<th>Abiraterone/prednisone (COU-AA-301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PSA at baseline (ng/ml)</td>
<td>144</td>
<td>129</td>
</tr>
<tr>
<td>Presence of pain at baseline (%)</td>
<td>46</td>
<td>44</td>
</tr>
<tr>
<td>Presence of visceral involvement (%)</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>Two (or more) prior chemotherapies (%)</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Median overall survival (months)</td>
<td>15.1</td>
<td>14.8</td>
</tr>
<tr>
<td>Median time to disease progression (months)</td>
<td>8.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Median time to PSA progression (months)</td>
<td>6.4</td>
<td>10.2</td>
</tr>
<tr>
<td>PSA response rate (≥50% PSA decline) (%)</td>
<td>39</td>
<td>29</td>
</tr>
<tr>
<td>Objective response rate (%)</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Pain response rate (%)</td>
<td>9</td>
<td>44</td>
</tr>
</tbody>
</table>

PSA: Prostate-specific antigen.

To definitively evaluate the effect of sipuleucel-T on survival, a pivotal multicenter double-blind placebo-controlled randomized Phase III trial (IMPACT) was conducted in men with asymptomatic or minimally symptomatic metastatic CRPC \[36\], leading to the FDA-approval of this agent in April 2010. In this trial, 512 patients were randomized (2:1) to receive either sipuleucel-T or placebo. Patients receiving placebo underwent leukapheresis of peripheral blood mononuclear cells, but these cells were cultured in growth medium that did not contain the GM-CSF-PAP fusion protein. Only 14% of men had received prior treatment with docetaxel chemotherapy. In addition, this study notably excluded men with visceral metastatic disease as well as men who were taking narcotics for cancer pain or immunosuppressive agents. Median overall survival was 25.8 in the sipuleucel-T group versus 21.7 months in the placebo group (HR: 0.78; p = 0.03), despite 64% of patients on placebo crossing over to receive salvage sipuleucel-T (prepared from cryopreserved antigen presenting cells collected at the time of placebo preparation). In the subset of patients with prior randomized 98 men with asymptomatic CRPC to either sipuleucel-T or placebo also failed to show a statistically significant improvement in progression-free survival, and a survival benefit was not demonstrated either. Encouragingly, however, a post hoc pooled analysis of these two trials (n = 225) suggested a survival advantage for the immunotherapy product, with a median survival of 23.2 months for patients receiving sipuleucel-T and 18.9 months for men receiving placebo (hazard ratio 0.67; p = 0.01) \[35\]. Adverse events related to sipuleucel-T in these studies were generally mild and included fever, chills/sweats, myalgias and headache. These reactions usually occurred during, or shortly after, infusion of the immunotherapy.

Multiple clinical trials using this personalized prostate cancer immunotherapy have been conducted. In a randomized Phase II/III study comparing sipuleucel-T against placebo in 127 men with asymptomatic metastatic CRPC, the immunotherapy did not achieve its primary end point of improving progression-free survival. Intriguingly, however, the study showed an improvement in median overall survival favoring sipuleucel-T over placebo (25.9 vs 21.4 months; HR: 0.59; p = 0.01) \[34\]. A second Phase II/III trial that
docetaxel treatment, overall survival trended in favor of sipuleucel-T, but this effect was not statistically significant. Therefore, although this immunotherapy is approved for all patients with asymptomatic, or minimally symptomatic CRPC, it will likely have its largest impact in the prechemotherapy setting.

Similar to previous studies with sipuleucel-T, the IMPACT trial found no difference in progression-free survival between the two treatment arms \[36\]. Some investigators attribute the discordance between progression-free and overall survival to a possible class effect of immunotherapy agents, relating to their mechanism of action which is distinct from cytotoxic therapies. To this end, a similar phenomenon was observed in a study using a PSA-directed poxviral-based immunotherapy product in men with metastatic CRPC (see next section) \[37\]. Problematic end points such as progression-free survival in CRPC (which may be confounded by both PSA and bone scan flare or delayed-onset effects) may perhaps be better addressed by revised guidelines using end points that are tailored to immunotherapeutic agents \[38\]. Such immunologically oriented end points will need to take into account standardization and harmonization of cellular immune response assays across different sites, novel patterns of clinical antitumor responses not captured by RECIST, and the effect of delayed separation of survival curves in Kaplan–Meier analysis.

**ProstVac-VF**

Another immunological approach for prostate cancer involves the use of viral vectors, such as attenuated vaccinia viruses. These vectors have the advantage of being able to deliver relatively large target payloads, and are easier to synthesize and produce than sipuleucel-T \[39\]. Early in the development of vaccinia-based vectors, it was noted that additional immunizations did not seem to result in added immunity against the target antigen but rather induced immunity against the viral components of the vector itself. Therefore, a heterologous prime-boost strategy was adopted, in which both the vaccinia and fowlpox vectors were used to produce long-lasting immune effects. For example, in a randomized Phase II trial, it was shown that vaccinia priming followed by a series of fowlpox booster treatments resulted in optimal cellular antitumor immune responses \[40\]. In addition, long-term follow-up of patients in that trial suggested a trend towards increased progression-free survival in men with advanced prostate cancer treated with the vaccinia prime/fowlpox boost strategy.

Poxviral vectors have been further refined using a platform of recombinant PSA inserted into vaccinia and fowlpox viral vectors (designated rV-PSA and rF-PSA, respectively), resulting in an immunotherapy product known as ProstVac-VF. ProstVac-VF consists of these constructs of rV-PSA and rF-PSA and also contains a triad of costimulatory molecules known as TriCom (intercellular adhesion molecule-1, B7–1, and leukocyte function-associated antigen-3) that serve to augment immune responses \[41\]. A Phase I study using a priming dose of ProstVac-VF followed by a booster dose four weeks later in 10 chemotherapy-naive patients with CRPC produced minimal toxicities and resulted in stable PSA levels lasting 8 weeks in four men \[42\]. Adverse events of this vaccine included injection-site reactions, pruritus, fevers/chills and fatigue. A randomized, double-blind Phase II trial of ProstVac-VF (consisting of one priming dose, followed by six booster doses over 24 weeks) versus empty vector in 122 men with metastatic CRPC failed to show a significant difference in the primary end point of progression-free survival between treatment arms \(p = 0.60\) \[43\]. However, long-term results of this trial revealed an overall survival benefit favoring the ProstVac-VF arm (median survival 25.1 months vs 16.6 months; \(p = 0.006\) \[37\]). Since survival was a secondary end point in this trial, these findings should be considered as hypothesis-generating only. Nevertheless, a randomized Phase II cooperative group study using docetaxel with or without ProstVac-VF as first-line therapy in 144 men with metastatic CRPC has recently been launched. In this trial, ProstVac-VF will be administered 12 weeks before docetaxel in the combination arm, while men in the control arm will receive immediate docetaxel alone. This study will use overall survival as its primary end point.

**Ipilimumab**

An alternative immune-directed strategy that has received recent attention involves inhibition of immunological checkpoints. Due to ongoing host immunological pressures on evolving tumors, cancers have developed several mechanisms to escape immune surveillance, essentially inducing a relative state of immune tolerance \[44\]. One way to inhibit immunological evasion by tumor cells is through blockade of the immune checkpoint molecule CTLA-4 (cytotoxic T lymphocyte-associated antigen-4) using monoclonal antibodies. CTLA-4 is a cell surface protein expressed by tumor-infiltrating T lymphocytes that functions as a negative regulator of T-cell activation, leading to attenuation of antitumor T-cell responses \[46\]. In murine prostate cancer models, CTLA-4 inhibition has previously been shown to potentiate T-cell effects and induce tumor rejection as well as reduce metastatic recurrence after primary prostate tumor resection \[46\], providing preliminary evidence that immune checkpoint blockade may be a useful approach.

Several clinical trials using the anti-CTLA-4 antibody, ipilimumab, have been conducted in men with metastatic prostate cancer.
CRPC. These include Phase I and II studies of ipilimumab monotherapy or in combination with radiation [47,48], as well as a Phase I dose-escalating study combining ipilimumab with GM-CSF [49]. Encouragingly, a few PSA reductions, as well as radiological tumor responses, were observed in all of these trials. Furthermore, ipilimumab in combination with PSA-TRICOM (a vector-based vaccine that targets PSA) in a Phase I study has shown prolongation of overall survival compared with Halabi predicted survival, suggesting augmentation of the effect of vaccine approaches by immune checkpoint inhibition [50].

Another Phase I study testing the combination of ipilimumab with a GM-CSF-secreting allogeneic cellular prostate cancer immunotherapy (GVAX) also demonstrated objective clinical responses at upper dose levels [51]. These results are particularly interesting, due to bona fide PSA and tumor responses rarely being reported in the immunotherapy trials discussed in the previous sections (e.g., using sipuleucel-T or Prostvac-VF). Common adverse events with ipilimumab include fatigue, rash, pruritus, nausea, constipation and weight loss. In addition, because in a normal host CTLA-4 serves to protect against autoimmunity, immunological toxicities resulting from an unchecked and overactive immune response may occur. Such severe immune-related adverse events include adrenal insufficiency, hepatitis, autoimmune colitis and even hypophysitis [52].

To investigate the impact of ipilimumab on overall survival, a multicenter placebo-controlled randomized Phase III study in patients with docetaxel-refractory CRPC has been launched, which aims to examine the combination of ipilimumab and radiation therapy in men with bone metastases. A total of 800 patients will first receive palliative radiation therapy to a bone lesion, and will then be randomized (1:1) to intravenous ipilimumab or placebo infusion given every 3 weeks. This trial is somewhat innovative in that it incorporates low-dose radiotherapy prior to the immunotherapy in an effort to prime an antitumor immune response against all sites of metastatic disease through release of antigen from irradiated tumor cells. Encouragingly, a Phase III trial in patients with metastatic melanoma has recently shown a survival advantage with the use of ipilimumab [53], providing a proof-of-principle that CTLA-4 blockade may have merit in human cancers and leading to the FDA-approval of this agent for melanoma patients. Thus, CTLA-4 blockade and other immune checkpoint blockades (such as PD-1 blockade [54]) are emerging as potential therapeutic strategies in CRPC, in which the overall risk/benefit ratio of induced autoimmunity versus antitumor activity will need to be evaluated carefully in the context of controlled clinical trials.

**Bone targeting therapy**

Causes of skeletal complications in men with metastatic prostate cancer are twofold: firstly, chronic androgen deprivation increases bone resorption and reduces bone mineral density. Secondly, bone involvement is extremely common and occurs in up to 75% of patients with metastatic disease. Complications of bone metastasis include bone pain, hypocalcemia of malignancy, SRE, such as fracture, need for radiation or surgery to bone, or spinal cord compression.

Until recently, aside from systemic chemotherapy targeting the malignancy itself, bisphosphonates remained the mainstay of adjunctive treatment to help maintain skeletal integrity in patients with metastatic prostate cancer. Benefits of bisphosphonates were shown definitively in patients with metastatic CRPC in a landmark Phase III study involving 643 men with CRPC and asymptomatic or minimally symptomatic bone metastases in which zoledronic acid was compared with placebo [55]. This study showed fewer SREs in the zoledronic acid group compared with placebo group (33.2 vs 44.2%; p = 0.021) and an increased median time to first SRE (488 vs 321 days; p = 0.009). More recently, denosumab, a monoclonal antibody that blocks receptor activator of nuclear factor-κB ligand (RANKL), has gained FDA approval for prevention of SREs in metastatic disease with bone involvement as a result of a large Phase III randomized trial which indicated its superiority over zoledronic acid in delaying time to first SRE in CRPC patients with bone metastasis [56]. Furthermore, radium-223, a bone seeking radionuclide, has recently been reported to have met its primary end point in a Phase III study, prolonging overall survival in castrate refractory prostate cancer patients [57,101].

**Denosumab**

Denosumab is a fully human monoclonal antibody to RANKL, a member of the tumor necrosis factor family that binds to RANK on immature and mature osteoclasts and thereby mediating differentiation, function and survival of osteoclasts. By blocking the binding of RANKL to RANK, denosumab effectively inhibits osteoclastic activity and thus osteoclast-mediated bone resorption. Denosumab was developed to treat patients with skeletal diseases mediated by osteoclasts such as bone metastasis, multiple myeloma and hormone ablation-induced bone loss in patients with cancer [58].

Bone metastasis in prostate cancer is thought to be dominated by an osteoblastic process. However, studies showed an equal importance of osteolytic/osteopenic processes mediated by osteoclasts as evidenced by increased serum and urinary N-telopeptide, a marker of increased bone resorption. A randomized
Phase II trial was conducted in patients with bone metastasis from prostate cancer, breast cancer or other neoplasms with elevated urinary N-telopeptide, despite bisphosphonate therapy [59]. Denosumab normalized urinary N-telopeptides levels more frequently than did continuation of bisphosphonates. Furthermore, patients receiving denosumab experienced fewer on-study SREs than those receiving bisphosphonates by the completion of the study. Subsequently, a multicenter randomized Phase III trial involved 1904 patients and compared denosumab 120 mg sq every 4 weeks to zoledronic acid 4 mg iv. every 4 weeks [56]. Randomization was stratified by previous SRE, PSA concentration and chemotherapy for prostate cancer with 6 weeks before randomization. The primary end point was time to first on-study SRE (pathological fracture, radiation therapy, surgery to bone or spinal cord compression), and this outcome was assessed for non-inferiority. The same outcome was further assessed for superiority as a secondary end point. At the time of the efficacy analysis, 950 men assigned to denosumab and 951 assigned to zoledronic acid were eligible for analysis. Median duration on study was 12.2 months for patients on denosumab and 11.2 months for those on zoledronic acid. Median time to first on-study SRE was 20.7 months (95% CI: 18.8–24.9) with denosumab compared with 17.1 months (15.0–19.4) with zoledronic acid (HR: 0.82; 95% CI: 0.71–0.95; p = 0.0002 for non-inferiority; p = 0.008 for superiority). As a result of this study, denosumab gained approval by the FDA for use in patients with bone involvement from prostate cancer as well as other solid tumors. Furthermore, recently reported is the survival advantage seen in a Phase III study evaluating another agent – radium 223 (alpharadin), a bone targeting radionuclide. A previous Phase II study showed superiority in all efficacy parameters including time to progression of PSA, bone alkaline phosphatase and median survival [57]. In June of 2011, a preplanned interim analysis of Phase III study evaluating radium 223 against placebo (ALSYMPCA) showed statistically significant (p = 0.0022; HR: 0.699) survival advantage.
for the radium-233 [101]. Based on this result, the study will be stopped per recommendation by the Independent Data Monitoring Committee and patients on the placebo arm will be offered treatment with radium-223. Regulatory approval will likely follow shortly which will expand bone-targeting treatment options for castrate refractory prostate cancer patients.

Future perspective
It is an exciting time for the prostate cancer research community. The approval of four new agents for CRPC in a one-year period is a watershed event for prostate cancer. This, coupled with a robust development pipeline of new agents (Figure 3), represents a substantial dividend obtained from investments in basic and translational research in prostate cancer over the last decade. A renewed interest in the AR axis, fueled by basic discoveries demonstrating the continued importance of AR signaling in CRPC, has led to the approval of one new agent and a deep pipeline of new agents targeting the AR axis that should see approval in the next few years. New insights into the mechanisms of CRPC adaption to low androgen conditions as well as a broader understanding of non-AR survival and growth pathways should lead to the development of additional therapeutic agents. The approval of Sipuleucel-T as the first vaccine shown to impact survival in a solid malignancy has spurred the clinical testing of additional vaccines for CRPC in large randomized trials. Basic and translational research in the area of immunotherapies has identified a number of other clinical candidates such as ipilimumab that may prove successful in prostate cancer.

While the approval of these new agents, and the ongoing development of many others has been met with great excitement by researchers and patients alike, each of these single agents have produced only modest survival benefits of a few months with responses of relatively short duration. More than 25,000 American men continue to die annually from CRPC while many more suffer from morbidity due to the disease. A major challenge, therefore, over the next 5–10 years will be to learn the way to use these agents most effectively, either sequentially or in combination to best impact survival. The extremely high cost of these newly approved agents (e.g., abiraterone acetate: US$5000/month; sipuleucel-T: $93,000/treatment) may prove to be a substantial impediment to the design and practical implementation of combination therapies in the future. Future research is likely to identify smaller subsets of patients who would best benefit from individual therapies based on genetic or epigenetic alterations within their particular tumors. The development of such ‘personalized therapies’ for CRPC, and cancer in general, is greatly anticipated but associated with inherent challenges that must be surmounted, for example, through new methods of trial design that overcome the current high cost of drug development, new imaging modalities to assess tumor response that correlate with overall survival and new methods to obtain tumor tissue for the required diagnostic studies. These challenges can be overcome through continued investment in innovative research in prostate cancer. However, this investment has recently been significantly diminished through cuts in the NIH research budget and the threatened elimination of the Department of Defense Prostate Cancer Research Program. Continued investment over the next decade is critical for continued success in the development of efficacious therapies for CRPC.

Executive summary

- Improved understanding of the biology of castration resistance and its subsequent application has led to significant advances in the therapeutic options in the treatment of castration-resistant prostate cancer (CRPC) in recent years.
- This past year has witnessed the approval of four different agents for the treatment of patients with metastatic CRPC.
- As much as 10% of total circulating testosterone originates from the adrenal glands and therefore the androgen axis continues to play an important part in the disease progression of CRPC.
- Abiraterone acetate is an irreversible inhibitor of CYP17,20 lyase which has shown a significant survival benefit postdocetaxel in a Phase III trial leading to its approval by the US FDA. Evaluation of its efficacy in the predocetaxel setting is ongoing.
- Cabazitaxel is a semi-synthetic taxane which has proven statistically significant survival benefit in docetaxel-refractory metastatic prostate cancer compared with mitoxantrone in a randomized Phase III trial leading to its approval by the FDA on 23rd April 2011. In light of the high incidence of neutropenia, alternative dosing of cabazitaxel is planned for investigation, as well as evaluation of cabazitaxel in the first-line setting.
- Sipuleucel-T has become the first therapeutic vaccine for any cancer by showing survival benefit in multiple Phase III trials. Sipuleucel-T gained its FDA-approval for asymptomatic or minimally symptomatic CRPC. Other promising immunotherapeutic agents on the horizon include ipilimumab and anti-PD-1 strategies.
- Denosumab is a RANKL which has shown superior time delay to SRE compared with zoledronic acid in a randomized Phase III study and has been approved for bone targeting therapy, in not only in prostate cancer, but also in other solid tumors with bone involvement.
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Bibliography


The unfolding treatment landscape for men with castration-resistant prostate cancer

Review: Clinical Trial Outcomes
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