The changing landscape in the treatment of metastatic castration-resistant prostate cancer

Joelle El-Amm and Jeanny B. Aragon-Ching

Abstract: The past few years have brought increasing advances in the therapeutic management of metastatic castration-resistant prostate cancer with the approval of several agents, including vaccine therapy with sipuleucel-T, second-line chemotherapy with cabazitaxel, the bone-targeted pharmaceutical denosumab, and the novel antiandrogen therapy abiraterone acetate. There are ongoing developments with other agents in the pipeline such as MDV3100 and alpharadin that have shown promising results. This review describes the clinical trials that brought about the drug approvals of various agents and offers some insights regarding a rational approach to optimal treatment sequencing for these drugs since national guidelines are currently lacking.

Keywords: Androgen deprivation therapy, chemotherapy, metastatic castration-resistant prostate cancer, vaccine therapy

Introduction
Prostate cancer remains the most common non-cutaneous malignancy among American men. In 2012 alone, about 241,740 cases will be diagnosed and about 28,170 will die from the disease [Siegel et al. 2012]. Increasing drug approvals have been made in the field of advanced prostate cancer ever since docetaxel was first approved for survival advantage in men with metastatic castration-resistant prostate cancer (mCRPC) based on the two pivotal trials, TAX-327 and SWOG 9916, which demonstrated superior overall survival (OS) outcomes in men treated with docetaxel and prednisone compared with mitoxantrone and prednisone in the frontline setting [Petrylak et al. 2004; Tannock et al. 2004]. In a disease state where the androgen receptor (AR) has previously been regarded as a nonrelevant target when castration resistance ensues, establishing the AR as a valid therapeutic target has come to the forefront with redefining terms such as ‘hormone resistance’ to ‘castration resistance’ [Attard et al. 2005]. In addition, median survival times reported from historical studies that ranged from about 6 to 10 months [Eisenberger et al. 1985] have now vastly improved in contemporary clinical trials, averaging 18–24 months or more. However, questions remain as to how to best sequence these agents and the emergent approval of all new therapies raise the question of appropriate clinical trial design in a disease state in which a multitude of drugs are showing OS improvements. Increasing efforts to better understand the mechanisms of actions and pathways of resistance are also crucial in developing alternative strategies for treatment of progressive castration-resistant prostate cancer (CRPC).

Recently approved agents
In this section we present pivotal trials that brought about US Food and Drug Administration (FDA) approvals for treatment of mCRPC (see Table 1).

Sipuleucel-T
Sipuleucel-T (Provenge, Dendreon, Seattle, WA, USA) was approved by the US FDA in April 2010 and is indicated for the treatment of asymptomatic or minimally symptomatic mCRPC based on the landmark IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) trial making it a first of its kind vaccine therapy approved...
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*Fast-track FDA designation.

FDA, US Food and Drug Administration; IMPACT, ImmunoTherapy for Prostate AdenoCarcinoma Treatment trial; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; SRE, skeletal-related event; TROPIC, Treatment of Hormone-Refractory Metastatic Prostate Cancer Previously Treated With a Taxotere-Containing Regimen trial.
for an advanced solid tumor [Kantoff et al. 2010a]. Sipuleucel-T is an autologous cellular cancer vaccine that is designed to stimulate an immune response to prostate cancer, consisting of peripheral blood mononuclear cells (PBMCs) obtained through leukapheresis from each patient and cultured in vitro for 2–3 days with PA2024, a prostatic acid phosphatase (PAP) fusion protein and granulocyte–macrophage colony-stimulating factor (GMCSF), inducing an immune response to PAP-expressing prostate cancer cells once the cells are reinfused [Higano et al. 2010]. Prior to the IMPACT trial, two initial phase III trials were conducted to study the efficacy of sipuleucel-T in patients with progressive mCRPC. The D9901 phase III placebo-controlled trial included 127 patients with progressive mCRPC who were randomly assigned in a 2:1 ratio to be treated with sipuleucel-T versus placebo [Small et al. 2006]. Although the study failed to meet its primary endpoint of median time to disease progression, median OS was significantly improved by 4.5 months in favor of sipuleucel-T (25.9 versus 21.4 months, \( p = 0.01 \)). D9902A was a double-blind, placebo-controlled trial of patients with asymptomatic mCRPC in which the study halted after 98 patients were enrolled given the findings of the D9901 study. Again, the combined analysis from D9901 and D9902A showed a significant improvement in OS in the sipuleucel-T group versus placebo (23.2 versus 18.9 months, \( p = 0.01 \)), though no improvement in median time to progression (TTP) was noted (11.7 versus 9.7 weeks, \( p = 0.111 \)) [Higano et al. 2009]. The IMPACT trial was therefore undertaken, a phase III, randomized, placebo-controlled study that enrolled 512 patients with asymptomatic or minimally symptomatic mCRPC with no visceral metastases. Patients were randomized to sipuleucel-T (\( n = 341 \)) versus placebo (\( n = 171 \)) in a 2:1 ratio with an OS seen in the experimental arm. The vast majority of patients were chemotherapy naive and all patients were required to be off corticosteroids for at least 4 weeks prior to study entry. The primary endpoint in this study was met with a median OS for the treatment arm improved by 4.1 months (25.8 versus 21.7 months, \( p = 0.03 \)), after a median follow up of 34.1 months. Similar to the preceding trials however, the secondary endpoints of time to objective disease progression, showed no statistical significance. In addition, hardly any prostate-specific antigen (PSA) responses were observed, with PSA reductions of at least 50% observed in 2.6% (8 of 311 patients) in the treatment group and 1.3% (2 of 153 patients) in the control group. Sipuleucel-T was generally well tolerated and most adverse events were generally mild or moderate in severity and usually resolved within 1–2 days, which led to hardly any treatment interruption occurring in only 0.9% of the patients, with most common toxicities related to the infusion.

Notwithstanding its beneficial effects, the exact mechanism of why sipuleucel-T works is yet unclear. It is believed that the survival advantage seen in the absence of significant PSA or tumor growth effects is because of changes in the biology over time. However, one emerging criticism lies in the scrutiny of the placebo arm of the IMPACT trial [Huber et al. 2012], such that the statistically significant effect on the overall population may have been driven by a skewed detrimental effect with poor survival in older patients (>65 years) in the placebo arm of the IMPACT trial. Nevertheless, the survival advantage seen with the use of sipuleucel-T lends credence to the utility of vaccine therapy as a valid therapeutic strategy in mCRPC.

**Cabazitaxel**

Cabazitaxel (Jevtana; Sanofi-Aventis, Paris, France) was approved by the US FDA in June 2010 as second-line therapy for patients whose condition has failed to respond to docetaxel. Cabazitaxel is a semisynthetic taxane that uses a precursor molecule extracted from yew tree needles. It inhibits microtubule depolymerization and cell division by binding to tubulin, resulting in cell cycle arrest. Its approval was based on the pivotal TROPIC trial (Treatment of Hormone-Refractory Metastatic Prostate Cancer Previously Treated With a Taxotere-Containing Regimen) [de Bono et al. 2010]. The TROPIC trial was a randomized, multicenter, multinational phase III trial that enrolled 755 men with mCRPC who progressed despite docetaxel-based chemotherapy. Patients were randomized 1:1 to receive either cabazitaxel 25 mg/m² or mitoxantrone 12 mg/m², both with prednisone 10 mg daily. A maximum of 10 cycles of treatment was mandated given the risk of mitoxantrone-induced cardiotoxicity. The protocol was amended to exclude patients previously treated with a cumulative docetaxel dose lower than 225 mg/m² (three cycles of docetaxel) to increase the likelihood of enrolling a true ‘docetaxel-refractory’ population. The primary endpoint of the study...
was OS. At a median follow up of 12.8 months, a 2.4-month median OS benefit was demonstrated for patients receiving cabazitaxel compared with mitoxantrone (15.1 versus 12.7 months; \( p = 0.0001 \)). Secondary outcomes that also favored cabazitaxel over mitoxantrone included progression-free survival (PFS) of 2.8 versus 1.4 months (hazard ratio (HR) 0.74, \( p < 0.0001 \)), tumor response (14.4% versus 4.4%, \( p = 0.0005 \)), PSA response (39.2% versus 17.8%, \( p = 0.0002 \)), time to tumor progression (8.8 versus 5.4 months, \( p < 0.0001 \)), and time to PSA progression (6.4 versus 3.1 months, \( p = 0.001 \)).

The most common clinically significant grade 3 or higher adverse events were neutropenia, which was more frequently observed in the cabazitaxel arm (82% versus 58%) and diarrhea, which was also more common with cabazitaxel (6% versus <1%). In addition, febrile neutropenia occurred in 8% of patients in the cabazitaxel group compared with 1% in the mitoxantrone group. In addition, a total of 18 deaths (5%) occurred in the cabazitaxel group, 7 of whom died of complications of myelosuppression, 5 died of cardiac etiology and 3 died of renal failure, compared with 2% of patients in the mitoxantrone group who died of adverse events. Based on the safety profile of cabazitaxel, it was concluded that administration of the drug requires careful monitoring, dose modification and prophylactic treatment with colony-stimulating factors in high-risk patients (age > 65, extensive prior radiation, serious comorbidities and poor nutritional status) [Pal et al. 2010].

Given the promising results of cabazitaxel, several questions have emerged and are being addressed in phase III trials, such as upfront use of cabazitaxel [ClinicalTrials.gov identifier: NCT01308567] and whether lower doses of cabazitaxel (20 mg/m²) will be noninferior with the standard approved dose of 25 mg/m² (PROSELICA) [ClinicalTrials.gov identifier: NCT01308580].

**Abiraterone acetate**

Abiraterone acetate (Zytiga; Janssen Biotech, Horsham, PA, USA) is a novel inhibitor of cytochrome P450 17 (CYP17), an enzyme responsible for steroid biosynthesis leading to production of androgenic and estrogenic steroids. Abiraterone acetate (AA) along with prednisone use attained approval from the US FDA in April 2011 for mCRPC after docetaxel failure based on the COU-AA-301 trial [de Bono et al. 2011]. The COU-AA-301 trial was a large randomized phase III trial that included 1195 patients with mCRPC whose condition progressed after docetaxel treatment. Patients were randomly assigned in a 2:1 ratio to receive prednisone 5 mg twice daily with either abiraterone acetate 1000 mg daily or placebo. Seventy percent of the patients had received one prior chemotherapy regimen and 30% had received two lines of prior chemotherapy. The primary endpoint was met with significant OS in the abiraterone acetate arm compared with the placebo arm (14.6 versus 10.9 months; HR 0.65; \( p < 0.001 \)) after a median follow up of 12.8 months. All secondary endpoints, including time to PSA progression (10.2 versus 6.6 months \( p < 0.001 \)), PFS (5.6 versus 3.6 months; \( p < 0.001 \)), and PSA response rate (29% versus 6%, \( p < 0.001 \)), favored the abiraterone acetate arm. Furthermore, pain responses were also seen. Since these results exceeded the preplanned criteria for study termination, data were unblinded at the interim analysis and patients were allowed to cross over to abiraterone acetate, with maintained improvement in OS with further updated analysis.

Abiraterone was well tolerated in the trial and most adverse events were grade 1 and 2 with fatigue being the most common followed by back pain, nausea, constipation, bone pain, and arthralgias. Given the CYP17 inhibition, adverse events associated with excess mineralocorticoid levels occurred more commonly in the abiraterone acetate arm compared with placebo, namely fluid retention (31% versus 22%, \( p = 0.04 \)) and hypokalemia (17% versus 8%, \( p < 0.001 \)).

The promising results of abiraterone acetate translate its value not only in the post-chemotherapy setting, in which it is currently approved, but to the pre-chemotherapy setting in the COU-302 study which included 1000 patients who had not received prior chemotherapy. The trial has completed accrual and the results have been shown to be promising [ClinicalTrials.gov identifier: NCT00887198].

**Denosumab**

Denosumab (Xgeva; Amgen, Cambridge, UK) is a fully human monoclonal anti-receptor activator of nuclear factor κB ligand (RANKL) antibody that was approved by the FDA in November 2010.
for the prevention of skeletal-related events (SREs) in patients with bone metastases from prostate cancer. There are varying etiologies for bone involvement in CRPC that encompasses reduced bone mineral density from castration treatment, glucocorticoid use and bone microenvironment changes related to the cancer itself [Roodman, 2004]. When cancer cells metastasize to the bone, their growth is promoted by growth factors as a consequence of osteoclastic bone resorption [Odero-Marah et al. 2008]. RANKL is a cytokine expressed in osteoblasts and bone marrow stromal cells and plays an important role in bone remodeling, and denosumab has been used in men with prostate cancer receiving hormone therapy to prevent bone loss [Smith et al. 2009].

A phase III, double-blind randomized noninferiority trial in men with bone metastases from mCRPC included 1904 patients who were randomly assigned in a 1:1 ratio to receive either subcutaneous denosumab 120 mg plus intravenous placebo or intravenous zoledronic acid 4 mg plus subcutaneous placebo every 4 weeks [Fizazi et al. 2011]. While there were no significant effects on PSA progression or OS, the trial met its primary endpoint of SRE prevention with median time to first on-study SRE of 20.7 months with denosumab compared with 17.1 months with zoledronic acid (HR 0.82, \( p = 0.0002 \) for non-inferiority, \( p = 0.008 \) for superiority). Common adverse events with the use of denosumab included hypocalcemia which occurred more frequently in the denosumab arm compared with the zoledronic acid arm (13% versus 6%, \( p < 0.0001 \)). Therefore, sufficient calcium and vitamin D levels must be reached before and during denosumab therapy. At the time of the analysis, osteonecrosis of the jaw occurred in 22 patients (2%) on denosumab versus 12 patients (1%) on zoledronic acid (\( p = 0.09 \)).

The main advantages of denosumab are the subcutaneous administration and the lack of renal dosing or toxicity [Aragon-Ching, 2011]. A phase III randomized, placebo-controlled trial (AFFIRM) has finished enrollment with a target accrual goal of 1199 patients in those who were treated with prior docetaxel [Scher et al. 2012]. Given the interim analysis showing that MDV3100 at a dose of 160 mg per day detected an OS difference in patients with mCRPC versus placebo by nearly 5 months (median OS 18.4 versus 13.6 months respectively, HR 0.631, \( p < 0.0001 \)), the trial was stopped early and MDV3100 was offered to patients assigned to placebo. Given these results, MDV3100 has been granted a fast-track designation by the FDA.

Similar to abiraterone, the use of these novel androgen-depleting agents has moved to the forefront in the prechemotherapy setting. A phase III trial (PREVAIL) looking at the use of MDV3100 in a chemotherapy-naïve population whose condition has failed to respond to androgen deprivation therapy (ADT) is currently ongoing with the results eagerly awaited.

**New agents on the horizon**

There are new and promising agents currently on the horizon for the treatment of mCRPC. This section discusses the agents that have progressed furthest in clinical trials.

**MDV3100**

MDV3100 (Enzalutamide; Medivation, San Francisco, CA, USA) is a novel androgen receptor signaling inhibitor that was developed for its high-affinity binding for the AR in comparison to bicalutamide and has the additional advantage of not promoting AR translocation to the nucleus or binding of AR to DNA and coactivator proteins [Tran et al. 2009]. An early phase I–II dose-escalation trial of MDV3100 in 140 patients with mCRPC showed antitumor effects at all doses, including decreases in serum PSA of 50% or more in 56% of the patients studied [Scher et al. 2010]. There were also responses in soft tissue in 22% of patients (13 of 59) and conversion from unfavorable (\( \geq 5 \) circulating tumor cells (CTCs)/7.5 ml of blood) to favorable (\(< 5 \text{ CTCs}/7.5 \text{ ml of blood} \)) CTC counts in 49% of patients (25 of 51). The median time for radiological progression was 47 weeks. The maximum tolerated dose of MDV3100 was 240 mg daily, with the most common adverse event being dose-dependent fatigue (observed in 11% of patients).

A phase III, randomized, international, multicenter, placebo-controlled trial (AFFIRM) has finished enrollment with a target accrual goal of 1199 patients in those who were treated with prior docetaxel [Scher et al. 2012]. Given the interim analysis showing that MDV3100 at a dose of 160 mg per day detected an OS difference in patients with mCRPC versus placebo by nearly 5 months (median OS 18.4 versus 13.6 months respectively, HR 0.631, \( p < 0.0001 \)), the trial was stopped early and MDV3100 was offered to patients assigned to placebo. Given these results, MDV3100 has been granted a fast-track designation by the FDA.
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**Alpharadin**

Radium-223 chloride ($^{223}$RaCl$_2$) is a first-in-class α pharmaceutical bone metastasis-targeting agent emitting high-energy α particles of short range. A multinational, phase III, double-blind, randomized study (ALSYMPCA) compared $^{223}$RaCl$_2$ plus best standard of care with placebo plus best supportive care in 922 patients with bony mCRPC [Sartor et al. 2012]. The study included men who had no known visceral metastases and had prior docetaxel (including docetaxel ineligibility or refusal) with progressive, symptomatic CRPC and at least two bone metastases on bone scan with the primary endpoint of the study being OS. Patients were randomized 2:1 ($^{223}$RaCl$_2$, $n = 615$; placebo, $n = 307$) to receive six injections of $^{223}$RaCl$_2$ (50 kBq/kg intravenously) every 4 weeks, meeting its primary endpoint of OS of 14 months versus 11.2 months in the placebo arm ($p = 0.00185$, HR = 0.695). Other secondary endpoints were also significant, such as SREs which were lower in the $^{223}$RaCl$_2$ versus placebo arm and time to first SRE, which was significantly delayed (median time to SRE 13.6 months versus 8.4 months respectively; $p = 0.00046$, HR = 0.610), findings reminiscent of the effects of other bone-targeted agents like denosumab. The toxicity profile of alpharadin was favorable, with low rates of grade 3 and 4 neutropenia (1.8% in the alpharadin arm versus 0.8% in the placebo arm) and thrombocytopenia (4% in the alpharadin arm versus 2% in the placebo arm). Based on these results, alpharadin has been granted a fast-track designation by the FDA. The study on $^{223}$RaCl$_2$ therefore heralds a new era with the use of radiopharmaceuticals as it is the first to show OS in a phase III randomized fashion.

**Other promising agents**

Several immunotherapy trials are currently underway that have shown promise, including a monoclonal antibody to cytotoxic T-lymphocyte antigen 4 immunotherapy, ipilimumab [Fong et al. 2009] as well as PROSTVAC-VF [Kantoff et al. 2010b], which comprises two recombinant viral vectors encoding transgenes for PSA, along with three immune costimulatory molecules (B7.1, intercellular adhesion molecule 1 and lymphocyte function associated antigen 3). Similarly, two phase III trials with ipilimumab are currently enrolling patients to a chemonaive [ClinicalTrials.gov identifier: NCT01057810] and a post-docetaxel trial, the latter being closed to accrual after completing enrollment [ClinicalTrials.gov identifier: NCT00861614]. Strategies targeting cell survival mechanisms such as OGX-011 or custirsen have emerged as an important target in prostate cancer therapy, especially in the context of delaying treatment resistance. Custirsen is an antisense oligonucleotide against clusterin, an antiapoptotic, stress-activated cytoprotective chaperone that confers treatment resistance when overexpressed [Chi et al. 2001; Miyake et al. 2000], and is already in phase III trials (SYNERGY trial) [ClinicalTrials.gov identifier: NCT01188187]. An earlier phase II randomized trial that enrolled 82 patients showed improved survival in the OGX-011 arm in combination with docetaxel as frontline therapy [Chi et al. 2010]. OS times were 23.8 months in patients who received docetaxel and prednisone along with OGX-011 versus 16.9 months in those who received docetaxel and prednisone alone. Another phase II trial in the post-docetaxel setting enrolled 42 patients who were randomized to receive docetaxel and prednisone with custirsen (DPC, $n = 20$) or mitoxantrone and prednisone with custirsen (MPC, $n = 22$) [Saad et al. 2011]. The results showed improved OS and time to pain progression in the DPC arm compared with the MPC arm of 15.8 and 10 months versus 11.5 and 5.2 months respectively, despite a lack of significant PSA or objective responses. OGX-427 is a second-generation antisense oligonucleotide that inhibits heat shock protein 27 (Hsp27), a relevant target in prostate cancer therapy since Hsp27 is a multifunctional chaperone protein implicated in cell signaling and cancer cell survival and progression. Hsp27 has been shown to complex with the AR, thus resulting in AR-regulated gene transactivation [Rocchi et al. 2004]. A randomized phase II trial using OGX-427 with prednisone showed improvement in PSA declines and partial response over prednisone alone [Chi et al. 2012].

Newer generations of antiandrogen signaling/synthesis inhibitors are also under study, including lyase inhibitors orteronel (TAK-700) [Kaku et al. 2011] and galeterone (TOK-001, formerly VN/124-1) [Handratta et al. 2005], and ARN-509 [Clegg et al. 2012], which has shown greater efficacy than MDV3100. Tasquinimod, a quinoline-3-carboxamide derivative that has
antiangiogenic effects and direct antineoplastic activity, has also shown promising effects. A phase II randomized trial enrolled 201 minimally or asymptomatic men with mCRPC in a 2:1 randomization with tasquinimod versus placebo. The trial showed improved PFS of 7.6 versus 3.3 months respectively [Pili et al. 2011], leading to a phase III randomized trial for patients with asymptomatic or minimally symptomatic mCRPC with radiographical PFS as the primary endpoint.

A new generation cell-signaling molecule inhibitor for hepatocyte growth factor receptor (MET) and vascular endothelial growth factor receptor 2 (VEGFR2), cabozantinib (XL184), has been shown in a randomized discontinuation phase II trial to result in objective responses with partial (56% of patients) or complete resolution (19%) of bone lesions. The results also showed 79% had stable disease by week 12 using response evaluation criteria in solid tumors (RECIST), with 4% having a confirmed partial response [Hussain et al. 2011]. The objective responses correlated with pain and bone turnover markers but not PSA. The promising results have led to two phase III trials that seek to determine pain palliation (COMET-2) [ClinicalTrials.gov identifier: NCT01522443] and OS (COMET-1) [ClinicalTrials.gov identifier: NCT01605227] in patients with mCRPC.

### Proposal for sequencing agents in metastatic castration-resistant prostate cancer

The rapid emergence of several promising agents that have shown improvement in OS in mCRPC has led to the question of how to sequence these varying agents from vaccine therapy to chemotherapy [Madan et al. 2011]. However, there is currently no level 1 evidence to guide clinicians regarding this matter. In clinical practice, the choice of initial agents often depends upon the clinical state of mCRPC. For the purpose of this review, we have stratified the clinical states of mCRPC into asymptomatic, minimally symptomatic or with rapid progression rate, overtly symptomatic and postdocetaxel chemotherapy (see Table 2). The addition of bone-targeting agents denosumab or zoledronic acid as part of treatment for men who have bony disease would also be paramount as part of supportive care.

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<td>Clinical trials, includes consideration for MDV3100 and alpharadin EAP</td>
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| **Mitoxantrone** |

| **Table 2. Proposed approaches to treatment of metastatic castration-resistant prostate cancer.*** |

*All phases may benefit from use of denosumab or zoledronic acid for bone metastases. EAP, expanded access program.

**Asymptomatic metastatic castration-resistant prostate cancer**

ADT has been the mainstay of firstline treatment for patients with advanced metastatic disease. As castration resistance ensues, alternative secondary hormonal manipulation was often instituted, such as the use of ketoconazole or second-line antiandrogens. While the majority of men with mCRPC would present with bony metastases, most tend to be asymptomatic. Thus, it is important to provide the opportunity for utilizing immunotherapy or vaccine therapy when the disease burden is thought to be at its lowest and when immune response is potentially at its greatest, given the lack of prior therapy that could dampen immune response (i.e. chemotherapy or steroids that are often employed in the treatment strategies). A closer look at the IMPACT trial shows that the separation of the curves was first apparent after about 6 months post therapy and was observed across all patients regardless of existing risk factors such as age, performance status, lactic acid dehydrogenase or Gleason scores. However, it should also be noted that about half of the men subsequently commenced
chemotherapy at a median of 12–13 months, suggesting that anticipation or need for chemotherapy perhaps in the next 6 months to a year should prompt the question regarding the appropriateness of institution of sipuleucel-T. This principle is also shown across other vaccine trials. For instance, in the National Cancer Institute PSA-TRICOM studies, patients were divided into those who have aggressive and indolent disease. Not surprisingly, those with a predicted Halabi nomogram survival of less than 18 months showed no marked improvement in survival while those who had a predicted Halabi nomogram survival of more than 18 months had a median survival that was not reached at the time of reporting [Gulley et al. 2010]. While the inherent mechanism of sipuleucel-T is not widely known, paradoxically improved survival in the absence of PFS or radiographic-free survival perhaps is a result of the effects on tumor progression kinetics, with slowed growth over time rather than immediate tumoral kill as evidenced with the use of cytotoxic chemotherapy [Madan et al. 2010]. Therefore, patients who exhibit aggressive disease would not be appropriate candidates for initial vaccine therapy, as the potential benefits from vaccine treatment tend to be delayed. Despite the data on improvement in the median OS, there are practical cost issues in implementing sipuleucel-T [Chambers and Neumann, 2011]. While a formal cost analysis for all the currently available treatments for mCRPC is not widely available, although possibly ultimately comparable when factoring in all potential adverse events management [Crawford and Flaig, 2012], the paucity in the production and manufacturing plants shows some disparity in the availability and actual number of patients eligible for this therapy [Peppercorn et al. 2012]. Therefore, sipuleucel-T is not readily available to all men who are otherwise eligible as it is not an ‘off-the-shelf’ vaccine. Alternatives, therefore, to the use of sipuleucel-T have emerged in the form of clinical trials utilizing vaccine or immunotherapy, including PROSTVAC and ipilimumab. Another important emerging therapy in this asymptomatic disease population is the use of novel AR targeting inhibitors or androgen synthesis inhibitors. While abiraterone acetate’s current FDA label is restricted to postdocetaxel administration, the abiraterone acetate COU-AA-302 trial, which enrolled 1088 chemotherapy-naïve patients, has been shown to also meet its trial endpoint of radiographic PFS with a strong trend for OS. Hence, the Independent Data Monitoring Committee has recommended unblinding of the trial with crossover of the placebo to the treatment group [Ryan et al. 2012b]. Abiraterone may soon be added to the armamentarium to treat this disease state. The MDV3100 trial PREVAIL is also accruing patients in the prechemotherapy setting and would be anticipated to have beneficial effects with the added advantage of not requiring steroids.

Asymptomatic metastatic castration-resistant prostate cancer with rapid progression rate

The timing of chemotherapy had always been a matter of debate [Hamberg et al. 2008] and with the advent of novel androgen therapies (including availability of abiraterone acetate pre-chemotherapy when insurance allows), the initiation of chemotherapy will likely become more protracted. One of the greatest concerns with the use of chemotherapy is the myelosuppression, especially in light of potential comorbidities. Therefore, chemotherapy is often reserved for the more symptomatic patients, for example, those with pain or with rapid progression rate, such as those with fast PSA doubling times. However, patients who have symptomatic disease tend to fare worse and the presence of pain confers a worse OS [Armstrong et al. 2007; Halabi et al. 2008]. In the TAX327 trial, patients who had no significant baseline pain also received a greater duration of therapy of 27 weeks (mean of 21 weeks) compared with men with a significant amount of pain who received only about 21 weeks of treatment (mean of 17.5 weeks), suggesting that having symptomatic pain at that point in time may compromise receipt of further therapy [Armstrong and George, 2010]. The role of chemotherapy has evolved in a manner such that clinicians have learned to stratify the disease process according to its presentation and symptoms, with men having symptomatic disease being offered chemotherapy while asymptomatic men are more inclined to be offered delayed chemotherapy by their physicians. It should be noted, though, that survival benefit from chemotherapy was seen in both symptomatic and asymptomatic patients. Although no single biomarker has been shown to confer superior diagnostic or prognostic accuracy, certain progression factors such as clinical deterioration, PSA doubling times, or use of biomarkers such as CTCs have been used in conjunction with well established clinical
parameters incorporated in nomograms [Halabi et al. 2003; Smaletz et al. 2002]. Evaluation of a subgroup of men from the TAX327 trial who had baseline PSA kinetics obtained before trial entry showed that men with rapid PSA doubling times (PSADTs) of less than 55 days were found to have increased likelihood of presenting with baseline pain, bone scan progression, lower hemoglobin and higher alkaline phosphatase compared with those with slower PSADTs [Armstrong et al. 2007]. While there is still marked heterogeneity among different disease states, PSADTs are easily obtainable and readily available for clinical use. The use of CTCs was initially confined to prognostication, such that men who have mCRPC who had unfavorable CTCs, defined as at least 5 CTCs/7.5 ml of blood had worse OS [Danila et al. 2007]. Similarly, men who convert from a poor prognostic factor to that of good prognostic factor also had improved OS post chemotherapy (i.e. prognosis for patients with unfavorable baseline CTCs who converted to favorable CTCs had improved survival from 6.8 to 21.3 months) [de Bono et al. 2008].

The importance of these clinical factors and biomarkers in prognostication and subject stratification has implications in choice of therapy, such that those with risk factors associated with independent predictors of death should be treated more aggressively.

**Symptomatic metastatic castration-resistant prostate cancer**

Upfront use of docetaxel has been the mainstay of treatment for patients who have symptomatic disease. The first chemotherapy that was approved was mitoxantrone in 1996, based upon palliative improvement of symptoms despite the lack of survival benefit [Tannock et al. 1996]. As with patients who exhibit rapidly progressive disease, the use of docetaxel has been deemed to be of most benefit, given the survival advantage seen in both the TAX327 and SWOG 9916 trials. The use of angiogenesis inhibitors in combination with docetaxel held some promise, with impressive PSA decline rates and objective tumor response [Ning et al. 2010], albeit with known but manageable adverse effects [Aragon-Ching et al. 2009]. However, enthusiasm for the use of angiogenesis inhibitors has been dampened when the results of a phase III, randomized, placebo-controlled CALGB trial showed that addition of bevacizumab did not confer survival advantage over that of standard docetaxel and prednisone alone [Kelly et al. 2012]. Perhaps enrollment of patients who had minimal disease burden, for whom the adverse effects of treatment from angiogenesis inhibitors along with toxic effects of chemotherapy far outweighed the benefits, may have had a role. Similarly, use of other angiogenesis inhibitors such as lenalidomide in a randomized, placebo-controlled phase III trial in combination with docetaxel and prednisone (MAINSAI) [ClinicalTrials.gov identifier: NCT00988208] was terminated prematurely after the data monitoring committee deemed futility in achieving its primary endpoint of OS.

Another strategy for patients with symptomatic pain would be the use of radiopharmaceuticals. Traditionally, samarium had been used for relief of metastatic bone pain [Sartor et al. 2004]. Despite its initial approval in 1997, samarium has not been widely adopted. Perhaps given its myelosuppressive effects, its use has been relegated to end-of-life palliation. The promising results of the α-emitting radiopharmaceutical alpharadin may change the landscape of treatment with the use of radiopharmaceuticals, especially given less myelosuppression as well as survival effects in addition to the palliation of pain [Liepe, 2009].

**Post-docetaxel metastatic castration-resistant prostate cancer**

Mitoxantrone has previously been the default standard of treatment post docetaxel failure [Aragon-Ching and Dahut, 2007]. However, since the approval of several agents post docetaxel, therapies have been geared towards analysis of further performance status and sequencing of agents. Varying mechanisms of taxane resistance have been studied, but there has been no consensus to date regarding a working definition of taxane resistance [Mathew and Dipaola, 2007]. Therefore, establishment of primary docetaxel resistance versus intolerance is helpful, since retreatment with docetaxel is feasible as a second-line therapy. Indeed, breaks in treatment schedules may be introduced in patients who particularly have initial response to docetaxel but who develop substantial or progressive toxicity. There does not appear to be significant differences in the OS between those who undergo
Continuous versus intermittent strategies [Lin et al. 2007].

Current FDA-approved therapies for postdocetaxel progression include cabazitaxel and abiraterone, although questions remain as to which therapy to use first in sequence [Beltran et al. 2011]. A closer analysis of both the TROPIC [de Bono et al. 2010] and COU-AA-301 [de Bono et al. 2011] trials showed similar median OS, although the comparator arm for the former was mitoxantrone and prednisone while only placebo with prednisone was used for the latter. In addition, there were about 25% of patients in TROPIC who had visceral metastases compared with about 10% in the COU-AA-301 trial. About 13% of patients in the TROPIC trial received two or more lines of chemotherapy while the COU-AA-301 trial excluded patients who had more than two prior chemotherapy regimens. Certain factors, such as baseline serum androgen levels, may predict response to abiraterone, such that those with higher baseline testosterone, androstenedione and dehydroepiandrosterenedione have better OS and response than those with lower baseline hormones [Ryan et al. 2012a]. There are currently no biomarkers or clinical parameters to predict who will benefit from which specific therapy first. Patients who had received prior ketoconazole were excluded from the COU-AA-301 trial but responses are still seen in abiraterone-treated patients who had prior ketoconazole [Ryan et al. 2010]. However, patients who have primary refractory disease on abiraterone would likely benefit from use of further cabazitaxel if performance status permits. It remains unclear whether patients who have responded on abiraterone should remain on the drug and have additive therapies rather than sequential treatment. Analysis of the toxicity profiles is relevant in the choice of further therapies, such that patients coming off docetaxel either due to resistance or intolerance may benefit from having a cytotoxic ‘drug holiday’ given the lack of myelosuppressive effects from abiraterone. Interestingly, palliative response from the use of cabazitaxel was not significantly different from that of mitoxantrone, whereas pain response was seen in the abiraterone trial. This certainly would be an area in which use of radiopharmaceuticals would be of benefit, especially in those with persistent pain from multiple bony metastases. This is also the phase where multiple clinical trials are currently available (see Table 3). MDV3100 will soon be available in this postdocetaxel setting as well as use of the radiopharmaceutical alpharadin, both currently available in expanded access programs in several institutions. Further treatment with vaccines or immunotherapy has been attempted and results for ipilimumab post chemotherapy are eagerly awaited. In patients who otherwise have good performance status, consideration for further sipuleucel-T may be given, since about 15% of patients in the IMPACT trial have received prior chemotherapy [Kantoff et al. 2010a]. However, patient selection is key given prior immunotherapy trials that showed potential harm when sipuleucel-T is used concurrently with chemotherapy [Small et al. 2009] as well as the premise that patients post chemotherapy may have blunted immune response from receipt of prior therapy or have disease that is biologically aggressive or resistant, such that little benefit may be gained [Slovin, 2012]. Ultimately, understanding the mechanisms of progression from novel androgen-targeting agents and lyase inhibitors [Cai et al. 2009; Mostaghel et al. 2011] will help in determining alternative off-target pathways that can circumvent progression.

Conclusion

The rapidly emerging field of prostate cancer therapeutics that brought about a dramatic change in the landscape of treatment in mCRPC is filled with excitement and anticipated challenge with rational sequencing or even combination therapy as the foremost question. Amidst all the new therapies that are currently available, the need for guidelines is all the more relevant to provide optimal opportunity for patients to see through the most effective treatment at the most appropriate time. Another ongoing challenge to drug development is choosing the appropriate comparator arm when designing clinical trials and whether PFS endpoints will be acceptable given approval of agents that have shown improvement in OS.

The current state of drug approvals in the field of prostate cancer is ever changing and while the sequencing is envisioned within the limits of the current FDA labels that each drug carries, the evolutionary changes that will ensue as more drugs get approved in prostate cancer will bring about further changes in the treatment paradigm of prostate cancer.
Table 3. Selected ongoing and completed phase III clinical trials in castration-resistant prostate cancer.

<table>
<thead>
<tr>
<th>Phase III trial</th>
<th>Arms</th>
<th>Patient population</th>
<th>Primary endpoints</th>
<th>Secondary endpoints</th>
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<tbody>
<tr>
<td><strong>Recruiting trials</strong></td>
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<tr>
<td>PREVAIL NCT01212991</td>
<td>MDV3100 versus placebo</td>
<td>mCRPC chemonaïve whose condition failed to respond to ADT</td>
<td>OS</td>
<td>Time to first SRE, time to cytotoxic chemotherapy</td>
</tr>
<tr>
<td>PROSPECT NCT01322490</td>
<td>PROSTVAC-V/F ± 6M-CSF versus placebo</td>
<td>Asymptomatic or minimally symptomatic mCRPC</td>
<td>OS</td>
<td>Event-free patients</td>
</tr>
<tr>
<td>SYNERGY NCT01188187</td>
<td>Docetaxel/prednisone versus docetaxel/prednisone in combination with 06X-011</td>
<td>mCRPC chemonaïve whose condition failed to respond to ADT</td>
<td>OS</td>
<td>PFS at days 140, 225; PSA measurements; safety</td>
</tr>
<tr>
<td>NCT01057810</td>
<td>Ipilimumab versus placebo</td>
<td>mCRPC chemonaïve whose condition failed to respond to ADT</td>
<td>OS</td>
<td>PFS, time to pain progression, time to subsequent treatment, safety</td>
</tr>
<tr>
<td>FIRSTANA NCT01308567</td>
<td>Cabazitaxel at 20 mg/m² or 25 mg/m² + prednisone versus docetaxel + prednisone</td>
<td>mCRPC chemonaïve whose condition failed to respond to ADT</td>
<td>OS</td>
<td>PFS</td>
</tr>
<tr>
<td>PROSELICA NCT01308580</td>
<td>Cabazitaxel at 20 mg/m² + prednisone versus cabazitaxel at 25 mg/m²</td>
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<tr>
<td>NCT00861614</td>
<td>Ipilimumab versus placebo</td>
<td>mCRPC post docetaxel</td>
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<tr>
<td>NCT01193257</td>
<td>Orteronel + prednisone versus placebo + prednisone</td>
<td>mCRPC post docetaxel</td>
<td>OS</td>
<td>50% PSA response at 12 weeks, pain response at 12 weeks, radiographical PFS</td>
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<tr>
<td>COMET-2 NCT01522443</td>
<td>XL184 versus mitoxantrone</td>
<td>Symptomatic mCRPC post docetaxel</td>
<td>Pain response at 12 weeks</td>
<td>Bone scan response, OS</td>
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<tr>
<td><strong>Completed trials</strong></td>
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<tr>
<td>MAINSAIL NCT00982088 (discontinued negative)</td>
<td>Lenalidomide + docetaxel + prednisone versus placebo + docetaxel + prednisone</td>
<td>mCRPC chemonaïve whose condition failed to respond to ADT</td>
<td>OS</td>
<td>PFS, ORR, safety</td>
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(Continued)
<table>
<thead>
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<th>Secondary endpoints</th>
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<tr>
<td>AA-COU-302 NCT00887198 (unblinded; positive)</td>
<td>Abiraterone acetate <em>versus</em> placebo</td>
<td>Asymptomatic or minimally symptomatic mCRPC, chemonaive</td>
<td>OS</td>
<td>Time to opiate use, cytotoxic chemotherapy use and PSA progression</td>
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<tr>
<td>VENICE NCT00519285 (negative)</td>
<td>Docetaxel + prednisone + aflibercept <em>versus</em> docetaxel + prednisone + placebo</td>
<td>CRPC in addition to docetaxel/prednisone</td>
<td>OS (primary endpoint was not met)</td>
<td>PSA measurement, pain, occurrence of SREs</td>
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<tr>
<td>NCT00286091 (positive)</td>
<td>Denosumab <em>versus</em> placebo</td>
<td>CRPC without bone metastasis (high risk for development of bone metastasis)</td>
<td>Bone metastasis-free survival</td>
<td></td>
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<tr>
<td>NCT01193244</td>
<td>Orteronel + prednisone <em>versus</em> placebo + prednisone</td>
<td>Chemonaive mCRPC</td>
<td>OS, radiographical PFS</td>
<td>50% PSA response at 12 weeks, change in CTC counts, time to pain progression</td>
</tr>
<tr>
<td>NCT00744497</td>
<td>Docetaxel + prednisone + dasatinib <em>versus</em> docetaxel + prednisone + placebo</td>
<td>mCRPC with docetaxel</td>
<td>OS</td>
<td>Tumor response rate, time to first SRE, time to PSA progression, PFS, safety</td>
</tr>
<tr>
<td>ENTHUSE-M1 NCT00554229 (negative)</td>
<td>Zibotentan <em>versus</em> placebo</td>
<td>mCRPC with bone metastasis, minimally symptomatic with no pain</td>
<td>OS</td>
<td>PFS, tolerability, incidence of SREs, bone metastases, time to PSA progression, time to pain progression, time to initiation of chemotherapy</td>
</tr>
<tr>
<td>NCT00134056 (negative)</td>
<td>Docetaxel + prednisone + atrasantan <em>versus</em> docetaxel + prednisone + placebo</td>
<td>mCRPC with bone metastasis</td>
<td>OS, PFS</td>
<td>Pain progression, toxicity, quality of life, PSA response</td>
</tr>
</tbody>
</table>

ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; GM-CSF, granulocyte macrophage colony-stimulating factor; mCRPC, metastatic castration-resistant prostate cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; SRE, skeletal-related event.
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**Conflict of interest statement**

Dr Aragon-Ching has served on the Advisory Board of Janssen/Ortho-Biotech, Sanofi-Aventis, and Amgen and has served on the Speakers’ Bureau of Janssen/Ortho-Biotech and Sanofi-Aventis.

**References**


