## Platinum Priority – Collaborative Review – Prostate Cancer
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# Castration-Resistant Prostate Cancer: From New Pathophysiology to New Treatment

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## Abstract

*Context:* Until recently, the only approved agent for metastatic castration-resistant prostate cancer (mCRPC) was docetaxel chemotherapy. But over the last 5 years, significant advances in the field have led to the approval of five new agents, each with different mechanisms of action and demonstrating improved overall survival in separate randomized phase 3 trials. Many of these novel agents are now also being evaluated in earlier stages of the disease, which may ultimately lead to even better outcomes.

*Objective:* To summarize the current literature on the management of mCRPC with a particular focus on novel chemotherapy approaches, hormonal approaches, immunotherapy, and radiopharmaceuticals showing survival benefits in phase 3 clinical trials. Emerging therapies in late stages of development are also discussed briefly.

*Evidence acquisition:* A comprehensive search of PubMed, identified studies pertaining to novel therapies evaluated in mCRPC since the initial approval of docetaxel in 2004. Abstracts from major international meetings were hand searched to identify studies of novel agents in late stage development in mCRPC. The Clinical Trials.gov database was used to find ongoing clinical trials in the area of mCRPC. A detailed search of each new agent was also performed to ensure that additional trials of these agents in other stages of the disease were included where relevant.

*Evidence synthesis:* The main agents discussed are the androgen synthesis inhibitor abiraterone acetate, the androgen receptor inhibitor enzalutamide, the novel taxane chemotherapy cabazitaxel, the immunotherapy sipuleucel-T, and the radiopharmaceutical radium 223. Other emerging agents and a brief discussion of negative phase 3 results are also included.

*Conclusions:* It is a very exciting time in the field of mCRPC, where therapeutic advances have improved outcomes in this disease, although once metastatic overall median survival remains a dismal 2–3 years. The key now will be to understand how best to use these new agents, understand the mechanisms of resistance to them, continue to develop novel treatment strategies, and ultimately test these agents earlier in the disease when cure may be possible.

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## 1. Introduction

In 2008, GLOBOCAN reported that worldwide prostate cancer (PCa) was the second most common cancer in men, behind lung cancer, accounting for 914 000 new cases and the sixth leading cause of cancer death with 258 000 deaths [1]. Notably, more than half of these cases occurred in developed countries such as Europe, North America and Australia. By 2030, it is estimated there will be 1.7 million new cases annually worldwide [2]. Over the last 5 years, age-adjusted PCa deaths have been decreasing, possibly due to a number of factors including (1) widespread use of prostate-specific antigen (PSA) testing (although highly controversial), (2) improvements in diagnostic testing, and in surgical and radiation techniques, and (3) increased use of androgen-deprivation therapy (ADT) following local treatment for high-risk disease.

Despite our best efforts at early diagnosis, aggressive treatment, and appropriate use of hormonal therapy, many patients eventually relapse. Disease progression despite castrate levels of testosterone is known as castration-resistant prostate cancer (CRPC) and can take the form of biochemical progression (elevated PSA only), radiographic progression (metastatic disease [mCRPC]), or symptomatic progression. In mCRPC, the only treatment until recently to show a survival benefit was docetaxel chemotherapy, but for patients progressing on or after docetaxel, options were limited and the prognosis was poor.

Over the last 5 years, however, several new agents tested in phase 3 clinical trials in mCRPC have not only shown improvements in overall survival (OS) but also symptomatic benefits and have significantly changed the treatment landscape in this disease (Table 1). Some of these new agents have now also been evaluated in the predocetaxel mCRPC setting or even earlier in the disease. It is hoped these new agents will drive death rates from PCa even lower, but in the meantime it is important to remember that none of these new agents are considered curative, strongly underscoring the need for ongoing research. In this review we discuss the main therapeutic advances, emerging agents, and the early sequencing trials aimed at understanding how best to select patients for these agents and how and when these agents should be used given the current data.

## 2. Evidence acquisition

A comprehensive search of PubMed from 2004 onward was performed. The main search terms were *prostate cancer, castrate-resistant prostate cancer, CRPC, abiraterone acetate, enzalutamide, cabazitaxel, sipuleucel-T, radium 223, phase 2, and phase 3*. In addition, a search of abstracts from all major meetings (European Society of Medical Oncology and American Society of Clinical Oncology) from 2004 onward with the main search term *prostate cancer* was also performed. All papers and abstracts discussing phase 3 trials in mCRPC, novel agents in late stage clinical development,

**Table 1 – Key phase 3 trials with new agents in metastatic castration-resistant prostate cancer**

| Drug | Clinical trial | Mechanism of action | Study design | Main inclusion criteria | Primary end point | Outcome |
|---|---|---|---|---|---|---|
| Abiraterone | COU-AA-301 NCT00638690 | Inhibits CYP-17 enzyme | Abiraterone plus prednisone vs placebo plus prednisone | mCRPC Docetaxel pretreated | OS | Improved OS Interim analysis: 13.8 vs 10.9 mo HR: 0.646 Final analysis: 15.6 vs 11.2 mo HR: 0.74 |
| Abiraterone | COU-AA-302 NCT00887198 | Inhibits CYP-17 enzyme | Abiraterone plus prednisone vs placebo plus prednisone | mCRPC Asymptomatic or mildly symptomatic No prior chemotherapy | PFS and OS | Improved PFS 16.5 vs 8.3 mo HR: 0.53 Trend to better OS 35.3 vs 30.1 mo HR: 0.79 Not statistically significant |
| Enzalutamide | AFFIRM NCT00974311 | Blocks the androgen receptor | Enzalutamide vs placebo | mCRPC Docetaxel pretreated | OS | Improved OS 18.4 vs 13.6 mo HR: 0.631 |
| Cabazitaxel | TROPIC NCT00417079 | Microtubule inhibitor | Cabazitaxel plus prednisone vs mitoxantrone plus prednisone | mCRPC Docetaxel pretreated | OS | Improved OS 15.1 vs 12.7 mo HR: 0.70 |
| Sipuleucel-T | IMPACT NCT00065442 | Dendritic vaccine | Sipuleucel-T vs placebo | mCRPC Asymptomatic or mildly symptomatic No prior chemotherapy | OS | Improved OS 25.8 vs 21.7 mo HR: 0.775 |
| Radium-223 (Xofigo) | ALSYMPCA NCT00699751 | Radiopharmaceutical α emitter calcium mimetic uptake into bone | Radium-223 vs placebo | mCRPC Symptomatic bone metastases No visceral disease Docetaxel unfit or pretreated | OS | Improved OS 14.0 vs 11.2 mo HR: 0.699 |

HR = hazard ratio; mCRPC = metastatic castration-resistant prostate cancer; OS = overall survival; PFS = progression-free survival.

and sequencing studies were extracted. The Clinical Trials.gov database was used to find ongoing trials in mCRPC, which are identified in the text with the trial identifier numbers in brackets. Key treatment approaches for mCRPC including hormonal therapy, chemotherapy, immunotherapy, and radiopharmaceuticals are outlined in detail in this paper.

## 3. Evidence synthesis

### 3.1. Hormonal therapy

The role of castration as a treatment approach in PCa has been well established since the initial observations by Huggins in 1942 [3]. However, it was only recently recognized that despite the development of castration resistance, many PCas remain dependent on androgen receptor (AR)-mediated signaling and activation of downstream genes [4,5]. In castration-resistant prostate cancer (CRPC), AR activation occurs through a number of different mechanisms including overexpression of the AR, de novo synthesis of intratumoral androgens, alterations in the AR or its cofactors such as AR splice variants, ligand-independent activation by growth factors or cytokines, or continued uptake of subcastrate levels of circulating androgens. The AR therefore remains an important target in CRPC [6,7].

#### 3.1.1. Abiraterone acetate

Abiraterone acetate (AA) is an oral irreversible inhibitor of the CYP-17 enzyme that blocks two critical steps in testosterone biosynthesis: conversion of pregnenolone to 17-OH pregnenolone and conversion of 17-OH pregnenolone to dehydroepiandrosterone. Inhibition of CYP-17 not only blocks androgen synthesis, but also blocks synthesis of glucocorticoids. This leads to a secondary rise in adrenocorticotropic hormone and excess mineralocorticoids. To prevent this, AA is coadministered with prednisone 5 mg twice daily [8–10]. In phase 1 and 2 studies there were no dose-limiting toxicities (DLTs) associated with AA, and the main side effects were hypokalemia and lower-limb edema (due to excess mineralocorticoids). Antitumor activity and PSA declines were seen at all dose levels and even in patients resistant to the related drug ketoconazole [11].

AA was evaluated in a randomized double-blind placebo-controlled phase 3 trial (COU 301) in 1195 mCRPC patients progressing despite prior docetaxel chemotherapy. Patients received AA 1000 mg daily on an empty stomach plus prednisone 5 mg twice daily (AA/prednisone) or prednisone alone [12]. The primary end point was OS. Treatment continued until clinical or radiographic progression, but a rising PSA alone was not considered adequate to indicate progression. At the time of a preplanned interim analysis, AA/prednisone showed a median OS of 14.8 mo compared with 10.9 mo with prednisone (hazard ratio [HR]: 0.65; 95% confidence interval [CI], 0.54–0.77; $p < 0.001$), leading to early trial closure after review by the Independent Data Monitoring Committee (IDMC). An updated OS analysis, conducted after 775 events, and before crossover from AA to placebo, demonstrated a median OS of 15.8 mo for AA/prednisone versus 11.2 mo for prednisone (HR: 0.74;

95% CI, 0.64–0.86). Key secondary end points including PSA response rate (RR), time to PSA progression, and radiographic progression-free survival (rPFS) were also significantly improved with AA/prednisone. In more than half the patients responding to AA/prednisone, bone scan flares were seen soon after initiating treatment. However, it was believed these discordant (early) bone scan results should not necessarily be interpreted as progression [13]. AA/prednisone was associated with improved pain and a delay of pain recurrence while preventing skeletal-related events (SREs) [14]. Toxicities including hypertension, edema, hypokalemia, atrial fibrillation, joint discomfort, and elevated liver function tests were more common with AA/prednisone, but grade 3 and higher toxicities were infrequent. Based on these results from COU 301, both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved AA/prednisone for mCRPC patients in the postdocetaxel setting in April and September 2011, respectively.

AA/prednisone was also tested in the prechemotherapy (chemotherapy-naive) setting. In the phase 3 COU 302 trial, 1088 asymptomatic mCRPC patients were randomized to AA/prednisone or prednisone [15]. After a second planned interim analysis when 43% of the expected deaths had occurred, the study was unblinded. AA/prednisone showed a median rPFS of 16.5 mo versus 8.3 mo with prednisone (HR: 0.53; 95% CI, 0.45–0.62; $p < 0.001$). Over a median follow-up of 22.2 mo, OS was improved with AA/prednisone (median not reached vs 27.2 mo; HR: 0.75; 95% CI, 0.61–0.93; $p = 0.01$) but did not cross the efficacy boundary for significance testing as defined by the O'Brien-Fleming cut-off. In February 2013, updated results showed an OS for AA/prednisone of 35.3 mo versus 30.1 mo for prednisone (HR: 0.79; 95% CI, 0.66–0.96; $p = 0.0151$). Again, OS favored AA/prednisone but did not cross the boundary for significance [16]. This could be partly due to the impact of therapies patients received after coming off the trial. AA/prednisone delayed time to initiation of cytotoxic chemotherapy, opiate use for cancer-related pain, SREs, PSA progression, and decline in performance status (PS). Grade 3 or 4 mineralocorticoid-related toxicities and abnormalities in liver function tests were more common with AA/prednisone but were low in both arms. Based on the COU 302 trial, both the FDA and EMA approved AA/prednisone for mCRPC patients in the predocetaxel or chemotherapy-naive setting in December and November 2012, respectively.

AA/prednisone was also evaluated in two small neoadjuvant studies (NCT00924469 and NCT01088529) where initial pathologic response rates appeared encouraging [17]. Studies of higher AA doses (2000 mg) and lower doses administered with food are also underway (NCT01637402 and NCT01543776). The latter study might have important implications, especially in jurisdictions where AA/prednisone is not covered or its cost is prohibitive. AA with lower doses of prednisone is also being evaluated. AA/prednisone in combination with hormonal agents like enzalutamide and ketoconazole, molecularly targeted therapies, immunotherapy, and other agents like the diabetic drug metformin are planned or ongoing at this time.

### 3.1.2. TAK-700 (Orteronel)

Based on the success of AA, it is clear that CYP17A is a viable target in mCRPC, which has generated interest in other CYP17A-inhibiting agents including TAK-700 (Orteronel), which is mechanistically similar to AA. TAK-700 inhibits 17, 20 lyase activity of CYP17A but does not inhibit 17-hydroxylase to the same extent, and therefore it may preclude the need for the coadministration of prednisone [18,19]. Two randomized placebo-controlled phase 3 studies of TAK-700 in mCRPC patients in the pre- and postdocetaxel settings have completed accrual, but both of these trials gave TAK-700 with prednisone, which negates the theoretical advantage of TAK-700 [20,21]. A phase 3 trial of TAK-700 without prednisone is now under way for high-risk PCa patients undergoing radiation and conventional androgen deprivation (RTOG 1115). TAK-700 will also be evaluated in non-mCRPC (NCT01046916).

### 3.1.3. Enzalutamide (previously known as MDV3100)

Enzalutamide is an oral high-affinity selective AR antagonist that potently binds to the AR, decreases ligand-induced nuclear translocation, inhibits AR binding to DNA, and blocks cell proliferation. Unlike AR antagonists such as bicalutamide, enzalutamide has no agonistic properties and shows preclinical activity even in bicalutamide-resistant prostate models. Clinical studies have confirmed both antitumor activity and tolerability. The most common toxicity is fatigue, which improved with dose reductions [22]. Notably, enzalutamide does not require the coadministration of prednisone because it has no effect on the steroid synthesis axis. In phase 1 studies, due to seizures noted in three patients at the 360-mg dose level, the 160-mg dose was taken forward. In the double-blind placebo-controlled phase 3 AFFIRM trial, mCRPC patients postdocetaxel were randomized 2:1 to receive enzalutamide or placebo. At the preplanned interim analysis, enzalutamide showed a 4.8-mo median OS benefit (18.4 mo vs 13.6 mo) compared with placebo ($p < 0.0001$), representing a 37% reduction in risk of death. The Independent Data Monitoring Committee (IDMC) suggested that the trial be unblinded and patients on placebo be crossed over to enzalutamide [23]. The most common side effects of enzalutamide were fatigue, diarrhea, and hot flashes. Five patients (0.6%) on enzalutamide were reported to have had seizures, whereas there were no seizures in the placebo arm. Based on the AFFIRM study, enzalutamide in the mCRPC postdocetaxel setting received FDA approval in August 2012 and EMA approval in April 2013.

In the double-blind placebo-controlled phase 3 PREVAIL trial, 1680 mCRPC patients predocetaxel were randomized to enzalutamide or placebo. This trial is fully accrued, and a preplanned interim analysis is expected in 2013. Enrollment also continues on two other trials directly comparing enzalutamide with bicalutamide in patients progressing on luteinizing hormone-releasing hormone analog monotherapy or following surgical castration. The STRIVE trial will enroll about 400 metastatic or nonmetastatic CPRC patients; the TERRAIN trial will enroll approximately 370 mCRPC patients. A neoadjuvant study with the goal of collecting correlative information is also underway [24,25]. Combination studies with abiraterone (NCT01650194) and docetaxel (NCT01565928) are ongoing or planned.

### 3.1.4. ARN-509

Building on the success of enzalutamide, ARN-509 is a novel small molecule AR antagonist. In the preclinical setting, ARN-509 has a better therapeutic index than enzalutamide that may allow the use of a lower active dose of the compound. In early studies, ARN-509 showed encouraging response rates and duration of response [26]. ARN-509 is being evaluated in mCRPC in the pre- and postchemotherapy settings and in a phase 2 study in non-mCRPC [27].

### 3.1.5. TOK-001

Another approach involves maximizing androgen blockade by combining a CYP-17 inhibitor and an AR antagonist. TOK-001 combines these two properties in a single drug and is in the early phase of development [28,29].

## 3.2. Chemotherapy

Historically, the role of systemic chemotherapy in mCRPC was questioned because patients often tolerated it poorly, and chemotherapy trials prior to 1991 reported low response rates and minimal clinical benefits. In the early 1990s, however, the role of chemotherapy in mCRPC was revisited with the development of better tolerated regimens that improved both quality of life and OS. Although overall rates of chemotherapy use have gone up, several studies suggest that it remains underutilized in mCRPC, which not only has an impact on survival but also access to other therapies in the postchemotherapy setting [30]. The first FDA-approved chemotherapy for mCRPC was mitoxantrone, a type II topoisomerase inhibitor, based on its palliative benefits despite a lack of improvement in OS [31]. The first chemotherapy to improve both quality of life and OS in mCRPC was docetaxel [32,33].

### 3.2.1. Docetaxel

Docetaxel is a taxane-based chemotherapy that binds and stabilizes tubulin, inducing cell cycle arrest and inhibiting cell proliferation. Docetaxel was evaluated in two pivotal randomized controlled trials: TAX 327 and SWOG 9916. In TAX 327, 1006 mCRPC patients received prednisone 5 mg twice daily and were randomized to docetaxel 75 mg/m$^2$ every 3 wk, docetaxel 30 mg/m$^2$ weekly, or mitoxantrone 12 mg/m$^2$ every 3 wk. Docetaxel every 3 wk showed a PSA RR (defined as ≥50% drop in PSA) of 48% versus 32% for mitoxantrone, and a median OS of 18.9 mo versus 16.5 mo [32]. In SWOG 9916, 770 mCRPC patients received prednisone 5 mg twice daily and docetaxel 60 mg/m$^2$ every 3 wk plus estramustine 280 mg three times daily or mitoxantrone 12 mg/m$^2$ every 3 wk. Again, PSA RR was higher (50% vs 27%) with docetaxel as was the median OS (17.5 mo vs 15.6 mo) [33]. Together these studies demonstrated the survival and symptomatic benefits of docetaxel over mitoxantrone, a drug now used in second or later lines or in first line for symptomatic patients who are

unfit for docetaxel. Given the similar efficacy of docetaxel in TAX 327 (without estramustine) and SWOG 9916 (with estramustine), and potential thromboembolic complications from estramustine, it is clear that estramustine has no additional benefit, so it is not used for mCRPC today. Docetaxel was FDA and EMA approved in 2004 for first-line mCRPC. Although in TAX 327, patients received up to 10 cycles of docetaxel, in routine clinical practice several studies suggest that patients may receive only about 7 cycles of treatment, highlighting the importance of having subsequent treatment options [34].

### 3.2.2. Cabazitaxel

Cabazitaxel is a novel semisynthetic taxane that also binds and stabilizes tubulin, inducing cell cycle arrest and inhibiting cell proliferation. It has shown preclinical activity in docetaxel-resistant models, although the mechanism by which this occurs is not clear. Cabazitaxel can penetrate the blood–brain barrier, which may have implications for brain metastases, although they are rare in PCa. In one early phase trial, the main DLT of cabazitaxel was neutropenia, and 20 mg/m$^2$ every 3 wk was the recommended phase 2 dose [35]; however, other non-published phase 1 trials recommended a dose of 25 mg/m$^2$, which was taken forward into the phase 3 TROPIC trial. This study randomized 755 mCRPC patients failing prior docetaxel to cabazitaxel (25 mg/m$^2$ every 3 wk) or mitoxantrone (12 mg/m$^2$ every 3 wk). Cabazitaxel significantly improved median OS compared with mitoxantrone (15.1 mo vs 12.7 mo; HR: 0.72; 95% CI, 0.61–0.84; $p < 0.0001$). Secondary end points including progression-free survival (PFS) (2.8 mo vs 1.4 mo), RR (14.4% vs 4.4%; $p = 0.005$), and median time to progression (TTP) by tumor assessment (8.8 mo vs 5.4 mo; $p < 0.001$) also favored cabazitaxel [36]. In a post hoc analysis, the survival benefit of cabazitaxel was maintained irrespective of whether prior docetaxel treatment was discontinued due to disease progression or not [37]. Febrile neutropenia, neutropenia, leukopenia, and diarrhea were more common with cabazitaxel. One concern with cabazitaxel was a treatment-related death rate of 5% compared with only 1.9% for mitoxantrone. A follow-up study has confirmed that the appropriate and timely use of GCSF prophylaxis reduces neutropenia, and it is recommended by the FDA for high-risk patients [38]. Cabazitaxel is FDA and EMA approved for mCRPC postdocetaxel. The FDA has also mandated two studies: a front-line three-arm study evaluating every 3 wk cabazitaxel (20 mg/m$^2$ and 25 mg/m$^2$) against docetaxel, which has now completed accrual, and a postdocetaxel two-arm study comparing cabazitaxel 20 mg/m$^2$ versus 25 mg/m$^2$. Other trials evaluating neoadjuvant cabazitaxel, weekly cabazitaxel, and combinations with other chemotherapy, targeted therapy, and immunotherapy, respectively, are in development.

### 3.3. Immunotherapy

Immunotherapy is an emerging strategy in mCRPC. One of the key challenges with immunotherapy remains determining how best to measure both the immune response and the antitumor activity and determine whether there is a correlation between these two factors. The immunotherapy agents most advanced in development include sipuleucel-T, PROSTVAC, and ipilimumab, but only sipuleucel-T is FDA approved for mCRPC. None of these agents are approved by the EMA.

### 3.3.1. Sipuleucel-T

Sipuleucel-T is a first-in-class dendritic cell-based vaccine that was FDA approved in April 2010 to treat asymptomatic or minimally symptomatic mCRPC. To prepare sipuleucel-T, a patient first undergoes leukapheresis to obtain the mononuclear cell fraction containing antigen-presenting cells (APCs). These are cultured for 36–44 h with a fusion protein (PA2024) composed of prostatic acid phosphatase (PAP), which is expressed by cancerous and noncancerous prostate cells, and granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator. Activated APCs, which express PA2024 antigens, are then reinfused into the patient to elicit an immune response. Sipuleucel-T is administered intravenously over 30–60 min, every 2 wk, for a total of three infusions [39].

Two small randomized phase 3 studies (D9901 and D9902A) comparing sipuleucel-T with control, and having a primary end point of TTP were initiated. Patients received either sipuleucel-T or control (made by culturing APCs without the fusion protein PA2024). Although neither study met with its primary end point of TTP, median survival in the sipuleucel-T arm was 4 mo longer than the control arm in both the D9901 study (25.9 mo vs 21.4 mo; $p = 0.01$) and in a pooled analysis of both studies (23.2 mo vs 18.9 mo; $p = 0.011$) [40,41]. The FDA requested that further data be obtained from a larger ongoing third phase 3 trial (9902B, also known as IMPACT). The IMPACT trial was a double-blind placebo-controlled multicenter phase 3 study in 512 patients with asymptomatic or minimally symptomatic mCRPC. Patients were randomized 2:1 to receive either sipuleucel-T or control, allowing crossover to a frozen sipuleucel-T–like product at disease progression. The median OS in the sipuleucel-T arm was 25.8 mo; in the control arm it was 21.7 mo, despite the crossover design. Immunologic studies showed a correlation between higher antibody titers against PA2024 and a prolonged survival ($p < 0.01$). However, there was no significant effect on PSA RR, radiologic responses, or TTP (14.6 wk vs 14.4 wk). Toxicities related to sipuleucel-T were mainly infusion-related chills, nausea, fever, headache, and fatigue [39]. Despite FDA approval, the uptake of sipuleucel-T has been slow. Costs, the cumbersome nature of the pheresis, and lack of changes in traditional end points such as PSA, objective response, or TTP are reasons often cited by investigators and clinicians alike for the lack of its use. Sipuleucel-T is currently under review by the EMA. Studies with sipuleucel-T aiming to better understand its mechanism of action, and how it should be sequenced with other mCRPC treatments, are ongoing. The ability to predict who is most likely to respond and determine

whether an effective immune response is achieved may increase the acceptability of this agent in mCRPC.

### 3.3.2. PROSTVAC

PROSTVAC-VF is a pox viral vaccine consisting of fowlpox and vaccinia vectors engineered to express the human PSA gene, and a triad of costimulatory molecules, including intercellular adhesion molecule 1, B7.1, and leukocyte function associated antigen 3, known as a triad of costimulatory molecules, or TRICOM [42]. PROSTVAC was evaluated in a randomized double-blind placebo-controlled phase 2 trial in chemotherapy-naive mCRPC patients, where PROSTVAC was administered as a priming dose followed by six boosts over a 24-wk period. As with sipuleucel-T, there was no difference in PFS or PSA RR, but there was an 8.5-mo median survival advantage with PROSTVAC compared with control (25.1 mo vs 16.6 mo; $p = 0.0061$) [43], although concerns have been raised about the particularly poor survival rates in the control arm, perhaps suggesting imbalances between the groups. A confirmatory phase 3 trial, PROSPECT, which will include 1200 chemotherapy-naive mCRPC patients and will compare PROSTVAC plus placebo versus PROSTVAC plus GM-CSF versus double placebo, is accruing. PROSTVAC is also being evaluated in earlier stages and in combination with docetaxel.

### 3.3.3. Ipilimumab

Another immunotherapy approach involves enhancing or prolonging T-cell activation by blocking immune checkpoint cytotoxic T lymphocyte antigen (CTLA)-4 receptors found on the surface of T cells that downregulate the T-cell response, mediating tumor-induced immune tolerance. The human monoclonal antibody ipilimumab is a checkpoint inhibitor that binds CTLA-4 and induces clinically important and durable tumor responses in patients with advanced melanoma where it is FDA approved. In PCa, ipilimumab has been evaluated in phase 1 and 2 trials in which notably both objective responses as well as PSA responses have been reported [44]. Two phase 3 trials randomizing between ipilimumab and placebo have completed accrual and results are pending for both chemotherapy-naive mCRPC and postchemotherapy mCRPC (NCT00861614 and NCT01057810).

### 3.3.4. Programmed cell death protein 1

Programmed cell death protein (PD)-1 is also a negative immune regulator expressed on the surface of activated T cells, B cells, and macrophages, and compared with CTLA-4, it may more broadly negatively regulate immune responses [45]. In many human tumors, PD-1 is upregulated, and increased expression has been associated with a worse clinical outcome. In PCa, CD8$^+$ T cells infiltrating the prostate gland commonly express PD-1, which may promote immune tolerance and allow cancers to develop without eliciting an immune response. PD-1–blocking antibodies may lift the immune tolerance and lead to an antitumor immune response. Anti–PD-1 antibodies are in early clinical trials, but little is reported in mCRPC [46,47].

### 3.4. Radiopharmaceuticals

Radium-223 (Ra 223) is a first-in-class radiopharmaceutical that is an α emitter and a calcium mimetic. Ra 223 is taken up into the bone (especially osteoblastic metastases), where it delivers high-energy, short-range α irradiation inducing DNA double-strand breaks. Unlike older agents such as samarium 153 and strontium 89, which are β-emitting radiopharmaceuticals, Ra 223 delivers high-energy but short-range radiation, limiting damage to normal tissues [48]. In the phase 3 Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) study, 921 mCRPC patients with bone metastases who were unfit for docetaxel or docetaxel pretreated were randomized to receive either Ra 223 or placebo. All patients continued on standard treatments including secondary hormonal therapies, bisphosphonates and analgesics, or radiation as required. Patients received six injections once every 4 wk over 6 mo. The primary end point was OS. Ra 223 was well tolerated and improved OS by 30%, 11.3 mo to 14.9 mo (HR: 0.695; $p = 0.00007$), and delayed time to first SRE [49]. Based on these results, Ra 223 was just approved by the FDA and is under review by the EMA.

### 3.5. Novel agents: some successes but also some failures

### 3.5.1. Negative phase 3 trials

Several drugs showing promising activity in phase 2 trials have shown disappointing phase 3 results (Table 2). Trials randomizing mCRPC patients to docetaxel or docetaxel with (1) bevacizumab, a monoclonal antibody to vascular endothelial growth factor (VEGF) [50], (2) Lenalinomide, an angiogenesis inhibitor similar to thalidomide [51], (3) aflibercept, a fusion protein of immunoglobulin G1 and VEGF receptor (VEGFR) 1 [52], (4) dasatinib, an Src inhibitor [53], (5) GVAX, a cell-based immunomodulatory agent [54], (6) DN101, a calcitriol derivative and highly active form of vitamin D [55], and both (7) atrasentan [56] and (8) zibotentan [57], which are endothelin A receptor antagonists, either failed to show improvements in OS or closed early due to futility. In patients previously treated with docetaxel, a phase 3 study of the angiogenesis inhibitor sunitinib with prednisone compared with prednisone alone also closed early for futility [58]. Whether these studies demonstrate a lack of efficacy of these agents in general or their ability to specifically improve on docetaxel remains unclear. Although negative, these studies add critical information to our understanding of this disease and help to direct future studies.

### 3.5.2. Novel agents in development

3.5.2.1. Cabozantinib. One of the most promising agents based on phase 2 data is cabozantinib, an oral agent targeting primarily c-MET and VEGFR2 but also RET, KIT (mast/stem cell growth factor), Flt-3 (FMS-like tyrosine kinase 3), AXL, and Tie-2 (tunica interna endothelial cell kinase [TEK] 2) [59]. In a phase 2 randomized discontinuation trial, 171 mCRPC patients received open-label cabozantinib for a12-wk lead-in period. Patients with stable disease were

**Table 2 – Key negative phase 3 trials with novel agents in metastatic castration-resistant prostate cancer**

| Drug | Clinical trial | Mechanism of action | Study design | Main inclusion criteria | Primary end point | Outcome |
|------|----------------|---------------------|--------------|-------------------------|-------------------|---------|
| Bevacizumab | CALGB90401 NCT00110214 | Targets angiogenesis antibody to VEGF | Bevacizumab plus docetaxel plus prednisone vs placebo plus docetaxel plus prednisone | mCRPC No prior chemotherapy | OS | Improved PFS 9.9 vs 7.5 mo but no improvement in OS |
| Lenalinomide | MAINSAIL NCT00988208 | Targets angiogenesis Immunomodulatory effects | Lenalinomide plus docetaxel plus prednisone vs placebo plus docetaxel plus prednisone | mCRPC No prior chemotherapy | OS | Closed early for futility in November 2011 |
| Aflibercept | VENICE NCT00519285 | Targets angiogenesis | Aflibercept plus docetaxel plus prednisone vs placebo plus docetaxel plus prednisone | mCRPC No prior chemotherapy | OS | No benefit Increased toxicity in the aflibercept arm |
| Dasatinib | READY NCT00744497 | Src inhibitor | Dasatinib plus docetaxel plus prednisone vs placebo plus docetaxel plus prednisone | mCRPC No prior chemotherapy | OS | No benefit |
| GVAX | VITAL-2 NCT00133224 | Immunomodulatory effects | GVAX plus docetaxel vs docetaxel plus prednisone | mCRPC Symptomatic No prior chemotherapy | OS | Closed early due to increased deaths in the GVAX arm in August 2008 |
| Calcitriol (DN101) | ASCENT 2 NCT00273338 | Bioactive vitamin D | Atrasentan plus docetaxel plus prednisone vs placebo plus docetaxel plus prednisone | mCRPC No prior chemotherapy | OS | Closed early due to increased deaths in the calcitriol arm in November 2007 |
| Atrasentan | SWOG 0421 NCT00134056 | Targets endothelin A receptor | Atrasentan plus docetaxel plus prednisone vs placebo plus docetaxel plus prednisone | mCRPC No prior chemotherapy | OS, PFS | Closed early for futility in April 2011 |
| Zibotentan | ENTHUSE M1C study 33 NCT00617669 | Targets endothelin A receptor | Zibotentan plus docetaxel plus prednisone vs placebo plus docetaxel plus prednisone | mCRPC No prior chemotherapy | OS | No benefit |
| Sunitinib | SUN1120 NCT00676650 | Targets angiogenesis | Sunitinib plus prednisone vs Prednisone | mCRPC Prior chemotherapy | OS | Closed early for futility in September 2010 |

mCRPC = metastatic castration-resistant prostate cancer; OS = overall survival; PFS = progression-free survival; VEGF = vascular endothelial growth factor.

randomly assigned to cabozantinib or placebo. The study was stopped early after cabozantinib showed an increased median PFS of 23.9 wk versus 5.9 wk with placebo. Most notably, complete or partial bone scan resolution was observed in 68% of patients. This correlated with a reduction in bone turnover markers, relief of bone pain, decreased narcotic use, soft tissue disease regression, and possibly improvement in quality of life. A post hoc analysis showed PSA changes did not correlate with the antitumor effects in bone and soft tissue, suggesting that PSA may not be a

reliable surrogate of clinical outcome in the context of treatment with cabozantinib. The most common toxicities were fatigue, hypertension, and dehydration, which were manageable with dose reductions [60]. Whether these impressive responses are due to targeting cMET or the combination of cMET and VEGF or other pathways independently is unclear (prior studies targeting the VEGF pathway were uniformly negative).

There are currently two phase 3 trials underway with cabozantinib. The first, COMET 1, is a randomized double-blind controlled study of cabozantinib versus prednisone in mCRPC previously treated with docetaxel and abiraterone or enzalutamide with a primary outcome of OS. The target accrual is 960, and the primary completion date is estimated to be March 2014 (NCT01605227). The second trial, COMET 2, is a randomized double-blind controlled trial of cabozantinib versus mitoxantrone plus prednisone in symptomatic mCRPC patients previously treated with docetaxel and either abiraterone or enzalutamide, with evidence of disease progression on each prior agent independently. Unlike other phase 3 studies, the primary end point of COMET 2 is a pain end point rather than OS. The target accrual is therefore smaller than traditional phase 3 studies, at 246, and estimated completion date is June 2014 (NCT01522443).

*3.5.2.2. Tasquinimod.* Tasquinimod is a dual angiogenesis inhibitor and immune modulatory agent. In a randomized placebo-controlled phase 2 study, in chemotherapy-naive mCRPC patients, the PFS with tasquinimod was 7.6 mo versus 3.3 mo with placebo ( $p$ = 0.0042), with OS also favoring tasquinimod at 34.2 mo versus 30.2 mo for placebo [61]. To confirm these results, a randomized double-blind placebo-controlled phase 3 study of tasquinimod in asymptomatic to mildly symptomatic chemotherapy-naive mCRPC patients has completed accrual of 1200 patients with final results expected in 2016.

*3.5.2.3. Custirsen.* Custirsen (formerly known as OGX-011) is an antisense oligonucleotide to the prosurvival protein clusterin. It was evaluated in a randomized phase 2 study, where 80 chemotherapy-naive mCRPC patients received docetaxel plus custirsen or docetaxel alone. Although PSA RR and PFS for both arms were similar, median OS in the custirsen arm was 23.8 mo versus 16.9 mo with docetaxel alone [62]. This led to a phase 3 trial (SYNERGY) of docetaxel plus custirsen versus docetaxel alone, which has completed accrual of 1000 patients with results expected at the end of 2013. Another phase 3 trial in the second-line setting comparing cabazitaxel alone with cabazitaxel with custirsen (AFFINITY), with a target accrual of approximately 630 patients and a primary end point of OS, is accruing with results expected at the end of 2015 (NCT01578655).

### 3.6. Sequencing of new agents

Over the last 5 years, the treatment landscape in mCRPC has changed significantly with the approval of several new drugs. The biggest challenge now facing clinicians is not a lack of treatment options but rather knowing how best to sequence or combine these new agents in a given patient. In the absence of large prospective sequencing trials to guide decisions, a number of important factors are considered. These include the clinical status of the patient (asymptomatic or symptomatic), burden of disease and rate of disease progression, presence of visceral or bony metastases, prior treatments and response, as well as drug-specific factors such as the mechanism of action, tolerability, and side-effect profile.

### 3.7. Asymptomatic chemotherapy-naive metastatic castration-resistant prostate cancer patients

In this setting, the COU-302 study has shown that AA improved PFS, and showed a trend toward improved OS. Depending on the results of the PREVAIL study, enzalutamide may also be an option in this setting. The main differences between AA and enzalutamide are the need to administer prednisone with AA and the marginal increase in seizure risk with enzalutamide. As these hormonal therapies move earlier in the treatment paradigm (before chemotherapy), an emerging question is whether the efficacy of subsequent docetaxel chemotherapy may be reduced. In a small trial by Mezynski et al., post AA, docetaxel showed lower activity and no responses in patients refractory to AA [63]. This could suggest cross-resistance between AA and docetaxel possibly due to the effect of docetaxel on AR nuclear transport [64], changes in the biology of the disease after AA, or simply that patients were more heavily pretreated. At the same time, this is a small retrospective study, so it is not possible to draw any firm conclusions, and larger prospective trials are needed.

Another option, in the predocetaxel setting for carefully selected patients, is sipuleucel-T. On the IMPACT study, most patients were asymptomatic or mildly symptomatic, had not received prior prednisone or chemotherapy, and although it did not improved OS, it did not have an impact on symptoms or delay disease progression. As such it is likely not an ideal treatment for symptomatic patients with rapidly progressive disease in need of an urgent tumor and/or symptomatic response. In terms of sequencing, one randomized trial evaluated sipuleucel-T before and after ADT and found that tumor-specific T-cell responses and immune responses were increased when sipuleucel-T was given after ADT rather than before [65]. Nonetheless, due to access and cost issues, sipuleucel-T is not a viable option for many patients.

### 3.8. Symptomatic metastatic castration-resistant prostate cancer patients postdocetaxel

For patients with more advanced symptomatic mCRPC, docetaxel has been the standard since 2004. Postdocetaxel, AA, enzalutamide, and cabazitaxel all improve OS, but how these agents should be sequenced is not clear and at this point is largely based on clinical judgment. Patients who are elderly, with a poor PS or those not tolerating docetaxel, may be best suited for either AA or enzalutamide largely because these agents are well tolerated, and although these patients are underrepresented in clinical trials, they did

derive symptomatic benefit from these agents over prednisone alone [66]. Young patients or those with a good PS, rapidly growing disease, or visceral metastases may benefit from cabazitaxel, with the option of subsequently receiving AA or enzalutamide. In a retrospective study of 42 postdocetaxel patients, Malik and colleagues found that patients who received cabazitaxel first were more likely to receive subsequent AA, than the converse, although the impact on PFS or OS was not yet known [67]. Another retrospective study of 125 postdocetaxel patients has shown similar results. Patients receiving cabazitaxel and then AA had improved OS compared with those receiving AA first [68]. In patients progressing after both docetaxel and enzalutamide, two studies showed that subsequent AA, although well tolerated, did show activity but not at the same degree of activity as seen on the COU-301 study [69,70]. Taken together, these early studies suggest that clinical cross-resistance may occur, and if confirmed may have important implications as the new hormonal agents move into the predocetaxel setting.

### 3.9. Patients with symptomatic bony disease, metastatic castration-resistant prostate cancer postdocetaxel, or docetaxel unfit

Finally, for patients with symptomatic bony metastases who are either unfit for docetaxel or docetaxel pretreated, Ra-223 is a potential option that has shown OS benefits [49]. As yet, it is unclear whether radium can be used in combination with any of the other agents or if it needs to be used alone.

At this point, larger prospective sequencing studies and combination studies incorporating standard end points, biomarkers, and correlative studies are urgently needed to understand both primary and acquired resistance mechanisms and inform clinicians on how best to sequence or combine these new agents to maximize benefit for patients.

### 4. Conclusions

Ultimately a better understanding of the molecular subtypes of PCa based on genomic and proteomic analysis as well as prognostic and predictive factors and biomarkers may help further improve the treatment of mCRPC, but to date, these studies are in their infancy. Clinical trials that are enriched for particular tumor or patient characteristics may prove to be helpful in personalizing treatments, but these studies have yet to be performed. With novel agents also comes the need to reevaluate standard clinical trial design and focus on end points that emphasize quality of life and attempt to incorporate validated biomarkers. As more and more drugs are approved, it will be essential to consider cost effectiveness prospectively and to determine on what basis these agents will be covered. Based on individual jurisdictions, some or all drugs, despite approval, may not be available to patients due to cost or other accessibility issues. It is indeed an exciting time in the field of PCa that has seen unprecedented advances, and it is poised to see more. It is important to continue the momentum with active enrollment to clinical trials to ensure that we maximize our knowledge of this disease.

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