Castration-resistant prostate cancer: new science and therapeutic prospects

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Abstract: There is a growing number of new therapies targeting different pathways that will revolutionize patient management strategies in castration-resistant prostate cancer (CRPC) patients. Today there are more clinical trial options for CRPC treatment than ever before, and there are many promising agents in late-stage clinical testing. The hypothesis that CRPC frequently remains driven by a ligand-activated androgen receptor (AR) and that CRPC tissues exhibit substantial residual androgen levels despite gonadotropin-releasing hormone therapy, has led to the evaluation of new oral compounds such as abiraterone and MDV 3100. Their results, coupled with promising recent findings in immunotherapy (eg sipuleucel-T) and with agents targeting angiogenesis (while awaiting the final results of the CALGB trial 90401) will most probably impact the management of patients with CRPC in the near future. Other new promising agents need further development. With our increased understanding of the biology of this disease, further trial design should incorporate improved patient selection so that patient populations are those who may be most likely to benefit from treatment.

Keywords: castration-resistant prostate cancer, chemotherapy, new agents, targeted therapies

Introduction

Castration-resistant prostate cancer (CRPC) has been used synonymously with androgen-independent (AIPC) and hormone-refractory prostate cancer (HRPC) but CRPC is the preferred and recommended term established by the Prostate Cancer Working Group 2 (PCWG 2) [Scher *et al.* 2008]. Docetaxel and prednisone (DP) were approved by the United States Food and Drug Administration (FDA) in 2004 for the palliative management of men with CRPC, based on improved survival, tumor response, pain and quality-of-life responses, in addition to tolerability [Tannock *et al.* 2004]. As such, the 3-weekly schedule of DP replaced mitoxantrone and prednisone (MP) as the standard of care in men with metastatic CRPC, and has become the backbone of current drug development in CRPC [Armstrong and George, 2008]. Despite docetaxel's approval as systemic therapy for metastatic CRPC and its adoption as the standard of care for CRPC patients [Petrylak *et al.* 2004; Tannock *et al.* 2004], median progression-free survival (PFS) remains about 6 months and overall survival (OS) remains less than 2 years. In current drug development, docetaxel has become the backbone as either a comparator and/or a foundation on which to add novel agents, and multiple efforts have been directed at improving its efficacy. Another development strategy is to test new agents in the docetaxel pretreated or refractory patient, for which there are no standard options.

In an effort to build on the demonstrated success of docetaxel, investigators have explored a broad range of traditional cytotoxic agents and novel-targeted molecules which may be additive or synergistic. Using cytotoxic drugs as a base on which to build, a series of recently-initiated trials are examining the efficacy and toxicity of the addition of molecularly-targeted agents and response modifiers. This has been termed the 'chemotherapy-plus' era of prostate cancer therapy [Bellmunt *et al.* 2009a]. These novel combinations may further slow progression and turn prostate cancer to a more chronic phenotype, possibly allowing patients to die with, rather than of, prostate cancer [Kalmadi and Raghavan, 2008].

With the recent discovery of novel pathways involved in prostate cancer progression, progress

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has been made in the understanding of the biology of CRPC based, at least in part, on the development of high-throughput technologies [Lin *et al.* 2005]. In addition, advances in immunology, angiogenesis, apoptosis, invasiveness and development of bone metastasis has helped to identify a number of potential therapeutic targets [Hadaschik and Gleave, 2007]. Unfortunately, even though compelling theories have been developed, as yet, none of the newer treatment modalities has yet been shown to be more effective than standard treatment. This review will discuss future approaches to systemic therapy in prostate cancer, including targeted approaches in late stage clinical development as well as phase III co-operative group trials (Table 1).

New chemotherapeutic agents

Efforts in the area of salvage chemotherapy have been focused on several classes of cytotoxic agents, including platinum agents (satraplatin, picoplatin), epothilones (ixabepilone, patupilone) and novel microtubule-targeting agents (XRP-6258) [Beardsley and Chi, 2008]. Preclinical data on satraplatin, a next-generation oral platinum, suggested activity in taxane-resistant prostate cancer cell lines [Armstrong and George, 2007]. In an aborted phase III trial launched by The European Organization for Research and Treatment of Cancer (EORTC) (comparing satraplatin plus prednisone *versus* prednisone) benefit in PFS was observed from 2.5 to 5.2 months ($p = 0.023$) in first-line treatment of HRPC [Sternberg *et al.* 2005]. An international, multicenter trial, the SPARC trial, was designed to test improvement in survival of satraplatin plus prednisolone compared with prednisolone alone. Preliminary findings showed a small but statistically significant improvement in PFS with satraplatin [hazard ratio (HR) 0.69, 95% confidence interval (CI) 0.6–0.8, $p < 0.001$] [Sternberg *et al.* 2005]. However, a subsequent analysis failed to detect a benefit on OS (median OS 61.3 *versus* 61.4 weeks for the satraplatin and control arms, respectively, HR 0.97, $p = 0.8$) [Sternberg *et al.* 2009a]. Satraplatin thus was not approved by the FDA, though efforts at evaluating possible clinical benefit continue.

Epothilones are a new class of tubulin-polymerizing agents that suppress microtubule dynamics similar in mechanism to that of taxanes, but are less susceptible to P-glycoprotein induced drug efflux [Bhandari and Hussain, 2005]. Mitoxantrone plus prednisone and ixabepilone each have modest, non cross-resistant activity as second-line chemotherapy regimens in docetaxel-refractory patients with CRPC. Phase II trials of the epothilone B analogue ixabepilone in patients with chemotherapy-naïve HRPC have shown PSA responses both in single agent therapy (33–48%) and in combination with estramustine (69%) [Rosenberg *et al.* 2007; Bhandari and Hussain, 2005; Hussain *et al.* 2005]. These agents were therefore combined in a phase I study [Rosenberg *et al.* 2009] which demonstrated significant anticancer activity and manageable tolerability, confirmed in a recently reported phase II trial at ASCO 2009 [Small *et al.* 2009a].

Overall, the lack of statistically significant benefit with initially promising agents like satraplatin has

Table 1. Categories of new therapies in castration-resistant prostate cancer.

Category	Examples
Targeting the androgen receptor	Androgen depleting agents: i.e. abiraterone (inhibitors of 17,20 lyase) New antiandrogens: MDV 3100 (preventing nuclear translocation and DNA binding of androgen receptor)
New chemotherapeutic agents	Satraplatin, epothilones
Differentiating agents	Vitamin D analogs (calcitriol)
Targeting growth factors/receptors pathways	Proliferative pathways: HER2, PI3K/Akt, mTOR, IGF Angiogenesis pathway: bevacizumab, lenolidamide, tyrosine kinase inhibitors (sunitinib, sorafenib) Apoptosis pathway: Bcl-2 antisense (oblimersen)
Active and passive immunotherapy	GM-CSF, sipuleucel-T, ipilumumab Prostvac®, GVAX®
Targeting epigenetics	Histone deacetylase inhibitors, antisense clusterin
Targeting the bone	Bisphosphonates, RANKL inhibitors, atrasentan, src family inhibitors, radiopharmaceuticals

Akt, protein kinase B; GM-CSF, granulocyte-macrophage colony-stimulating factor; HER2, human epidermal growth factor receptor 2; IGF, insulin-like growth factor; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3 kinase; RANKL, receptor activator of NF-kappaB ligand.

generated a decrease of enthusiasm for chemotherapy alone in this disease. This forms the rationale for moving towards biologic 'targeted' agents alone or in combination with chemotherapy.

Differentiating agents

Differentiation therapy with agents that reverse the dedifferentiation that accompanies the malignant phenotype, provide an alternative to conventional combination chemotherapy [Leibowitz and Kantoff, 2003]. *In vitro* studies have shown that calcitriol (1,25-dihydroxycholecalciferol) inhibits growth and promotes differentiation of prostate cancer cells [Vijayakumar *et al.* 2005]. DN-101 is a proprietary oral formulation of 1,25-dihydroxycholecalciferol, which is able to provide supraphysiological doses of vitamin D without side effects such as hypercalcemia. In addition to its differentiating properties in prostate cancer cell lines, calcitriol has also been shown to inhibit the growth, reduce invasion and angiogenesis, stimulate apoptosis and synergize with chemotherapy [Skowronski *et al.* 1993]. Docetaxel, prednisone, and DN-101 were evaluated in a randomized placebo-controlled phase II multi-institutional study (ASCENT-1) of 250 men with progressive CRPC [Beer, 2005]. Patients were randomized to receive weekly docetaxel alone or docetaxel combined with DN-101. While the primary endpoint of PSA response was not met, and the study was underpowered to detect survival differences; the estimated median survival was significantly prolonged, from 16.4 to 23.5 months in the unadjusted analysis (HR 0.70, $p < 0.07$), with a favorable toxicity profile [Beer *et al.* 2007].These results led to the initiation of the phase III ASCENT-2 trial comparing every 3 week docetaxel plus prednisone with weekly docetaxel plus DN-101. However, after recruitment of over 900 of the planned 1200 patients, the study was closed early by the sponsor because of a higher death rate in the docetaxel plus DN-101 arm [Chang and Kibel, 2009]. Although calcitriol generated much interest based on favorable preclinical data and phase II studies, after the discouraging results of the phase III trial, it remains that differentiating agents will not have an immediate role in the management of prostate cancer.

Targeting the androgen receptor

Continued androgen-receptor (AR) activation occurs, even in the setting of castrate levels of androgens, likely from one or more of several mechanisms including: amplification of the AR gene leading to hypersensitivity to ligand, receptor promiscuity *via* missense mutations of AR, transactivation by coactivators and direct activation by other pathways (insulin-like growth factor receptor, ERBB2 (epidermal growth factor receptor 2), and Akt (serine-threonine kinase) [Hsieh *et al.* 2007; Feldman and Feldman, 2001].

Continued (androgen-dependent) prostate-specific antigen (PSA) secretion and the presence in tumor samples of androgens and AR mRNA expression at levels associated with active AR signaling strongly suggest that reactivation of the AR and AR-responsive pathways is also one of the mechanisms by which tumors become resistant to androgen deprivation [Titus *et al.* 2005]. The peripheral conversion of adrenal androgenic steroids (primarily androstenedione) to testosterone by 17-ketoreductase could account for these intratumoral androgens although it has been hypothesized that altered regulation of tumor enzymes involved in the synthesis and inactivation of androgens may be one cause for their accumulation [Chen *et al.* 2009]. Prostate cancer cells also circumvent the effects of androgen blockade by developing the ability to use very low levels of androgen to proliferate. DNA amplification resulting in increased AR expression can result in a receptor capable of activation with low levels of ligand, further supporting AR signaling as a mechanism for castration resistance. In cell lines, increased expression of AR mRNA by less than twofold may result in resistance to anti-androgens [Chen *et al.* 2004]. There is therefore increasing evidence that a role may exist for novel strategies to target the AR and inhibit androgen synthesis, with the aim of creating an androgen-free environment in prostate tumors [Attard *et al.* 2006].

Based on the findings of persistent androgen signaling and adrenal androgen synthesis in CRPC, several novel anti-androgen and androgen synthesis inhibitors including abiraterone (a potent 17α-hydroxylase and C17,20-lyase inhibitor), and MDV-3100 [Tran *et al.* 2009] (a potent AR antagonist that prevents nuclear translocation and DNA binding of AR) are in clinical trials [Attard *et al.* 2009a; Chen *et al.* 2009]. Early exciting phase II results both pre- and postdocetaxel, have been reported with these agents in CRPC [Attard *et al.* 2009b].

In a phase I/II study of abiraterone acetate in castrate, chemotherapy-naive CRPC patients

($n = 54$) a decline in PSA of ≥50% was observed in 28 (67%) of 42 phase II patients, and declines of ≥90% were observed in eight (19%) of 42 patients. Independent radiologic evaluation reported partial responses (RECIST) in nine (37.5%) of 24 phase II patients with measurable disease [Attard *et al.* 2009b]. Similar data have been reported in another trial in patients not even exposed to ketoconazole [Ryan *et al.* 2009] with PSA declines of ≥30%, ≥50%, ≥90% in 89% (24/27), 85% (23/27) and 41% (11/27) patients, respectively. Abiraterone has also been tested in docetaxel-pretreated CRPC patients providing exciting results. In 47 CRPC patients, total maximal PSA declines of ≥30%, ≥50%, and ≥90% were observed in 32 (69%), 24 (51%) and seven (15%) patients respectively. Out of 35 patients evaluable by RECIST; six (17%) had a partial response and 23 (66%) had stable disease [Reid *et al.* 2009].

Recent results with MDV3100 have been reported. MDV was tested in 140 patients with castration-resistant prostate cancer showing PSA declines (>50% from baseline) at week 12 in 57% (37/65) of chemonaïve and in 45% (22/49) of postchemotherapy patients [Scher and Beer, 2009].

These novel anti-androgens and androgen synthesis inhibitors are now in phase III trials in CRPC, and in the case of abiraterone, a phase III trial in post-docetaxel treatment has completed accrual with results expected soon. Several new other agents [Attar *et al.* 2009] and strategies targeting the androgen pathway are emerging [Chen *et al.* 2009].

In the field of genomics linked to hormone therapy, two recent studies have shown that germline DNA polymorphisms can influence the response to androgen deprivation therapy (ADT). The first study was conducted in 529 patients with advanced prostate cancer with and without radiographic evidence of metastatic disease. The investigators examined 129 DNA polymorphisms associated with 20 genes that are involved in androgen metabolism and found that three single nucleotide polymorphisms (SNP) were significantly associated with response duration to ADT [Ross *et al.* 2008a]. A second study was based on preclinical work with SLCO1B3, a gene that codes for OATP1B3 (a protein that is a transmembrane transporter of testosterone and other steroids). SLCO1B3 has two SNPs in the protein coding region of this gene; 334T > G and 699G>. Expression of the allele containing 334T and 699G (T allele) confers an increase in testosterone uptake when compared to cells that express the 334G and 699A allele (G allele) [Hamada *et al.* 2008]. In an analysis of white patients with advanced prostate cancer with and without radiographic evidence of metastatic disease treated with ADT, patients with one or two copies of the T allele had a shorter time to CRPC compared with patients with two copies of the G allele [Hamada *et al.* 2008]. These two studies show evidence that SNPs in four genes are involved in the response duration to ADT. The utility of understanding germline determinants of the response to ADT is that this could be used, along with known and established clinical factors, before the administration of hormonal therapy, to prognosticate clinical course [Sharifi *et al.* 2008].

The perception with new ways of targeting the AR is that the current excitement in the field lies not only in the two new compounds at hand, but in future agents that are designed based on our increasing understanding of AR biology.

Targeting growth factor pathways

The growth and survival addiction to mutated oncogenic signaling pathways may be both the source of cancer progression and also a target to explore therapeutic interventions [Gregory *et al.* 2005; Weinstein, 2002]. Several investigational agents target pathways that appear important in prostate cancer pathogenesis, maintenance, and progression. These include therapies that target the human epidermal growth factor receptor 2 (HER2), the phosphatidylinositol-3 kinase (PI3K)/Akt, the mammalian target of rapamycin (mTOR), and the insulin-like growth factor (IGF)-1 pathways. Even though preclinical evidence supports the importance of these molecular pathways, clinical testing of most of these agents remains immature.

HER2

One potential target involved in cellular growth includes the HER2/neu (ErbB-2) tyrosine kinase. HER2 expression has been shown to increase AR activation leading to growth of prostate cells [Gregory *et al.* 2005]. Overall, overexpression of the HER2 receptor is not prevalent in prostate cancer (4%) [Morris *et al.* 2002], and clustered gene amplification in primary prostate cancer has rarely been found (2%) in large-sample studies

[Oxley *et al.* 2002]. These findings differ from studies of breast cancer, in which approximately 30% of patients overexpress the HER2 receptor, and the protein overexpression is highly correlated with gene amplification.

However, HER2-receptor expression appeared to increase with progression to androgen independence, thereby supporting therapeutic targeting of this molecule in HRPC [Signoretti *et al.* 2000]. Phase II studies with anti-HER2 monoclonal antibodies, trastuzumab and pertuzumab, treating all-comers have shown low levels of efficacy in CRPC, possibly due to this low prevalence of HER2 overexpression [de Bono *et al.* 2007; Canil *et al.* 2005; Ziada *et al.* 2004]. Currently, phase II studies are ongoing using the dual epidermal growth factor receptor (EGFR)/HER2 kinase inhibitor, lapatinib, in men with PSA relapse and CRPC specifically addressing the identification of biological correlates of response [Chen *et al.* 2008].

PI3kinase/Akt

Another potential target of advanced prostate cancer is PTEN (the tumor suppressor gene encoding phosphatase and tensin homolog deleted on chromosome 10) whose expression is lost in the majority cases [McMenamin *et al.* 1999; Wu *et al.* 1998]. Loss of PTEN leads to unrestrained activation of the phosphatidylinositide 3-kinase (PI3K)/Akt pathway and cellular survival signaling. PI3K is a complex heterodimeric molecule with multiple subcomponents, which receives upstream signals from multiple receptor tyrosine kinases, including the insulin-like growth factor receptor [Jiang and Liu, 2009]. Activation of the PI3K leads to Akt activation and translocation to the nucleus, where it in turn regulates diverse functions in the cell by protein phosphorylation. While no activating point mutations of Akt have been identified in prostate cancer specimens, high levels of Akt activity appear to be involved in prostate cancer growth and progression [Majumder and Sellers, 2005]. Increased Akt activity has been demonstrated in more poorly differentiated prostate tumors, predicting biochemical recurrence [Kreisberg *et al.* 2004; Malik *et al.* 2002], and has been implicated in the progression to castration resistance. *In vitro* studies with androgen-dependent LNCaP cells grown in the absence of androgens develop androgen independent growth and high levels of Akt activation [Murillo *et al.* 2001]. Akt activation was also increased in LNCaP xenografts grown in castrated mice, compared to the parental LNCaP cell line [Graff *et al.* 2000].

Akt and PI3K inhibitors are currently under investigation in clinical trials in prostate cancer. Perifosine, an oral Akt inhibitor, has been evaluated in a phase II study of patients with hormone-sensitive prostate cancer and rising PSA after definitive local therapy [Chee *et al.* 2007]. Twenty percent of patients had a reduction in PSA levels, but none had declines greater than 50%. PSA doubling time (compared to pretreatment doubling-time) was not increased with perifosine treatment, and the median time to PSA progression was 6.6 months. This modest activity was felt to be insufficient to justify further single-agent testing of perifosine in prostate cancer, but combination studies with ADT and chemotherapy are underway.

mTOR inhibition

One downstream target of PI3k/Akt pathway is the mTOR kinase, which is activated in phosphatase and tensin homolog (PTEN)-deleted tumors. mTOR is a serine/threonine kinase that receives signals from multiple upstream growth and nutrient sensing pathways, and phosphorylates transcription factors that are critical for cell proliferation (S6K1 and 4E-BP1) [Dunlop *et al.* 2009; Dunlop and Tee, 2009]. Preclinical testing suggests that Akt upregulation may be counteracted by mTOR inhibition. Transgenic mice expressing human Akt, develop tumors in the ventral prostate which are reversed when treated with everolimus, an oral mTOR inhibitor [Majumder *et al.* 2004]. Other preclinical work suggests that mTOR inhibition might restore chemotherapy sensitivity to resistant prostate cancer cell lines. PTEN-deficient PC-3 cells treated with rapamycin or temsirolimus were rendered sensitive to doxorubicin, similar to PC-3 cells with normal PTEN expression both *in vitro* and *in vivo* [Grunwald *et al.* 2002].

Agents targeting mTOR have been tested in phase II studies in prostate cancer, and phase I and pre-prostatectomy studies of these agents have demonstrated early signs of successful target inhibition [Garcia and Danielpour, 2008]. A pharmacodynamic study of everolimus was conducted in patients with newly diagnosed prostate cancer about to undergo radical prostatectomy [Lerut *et al.* 2005]. Preliminary results suggest that mTOR inhibition by everolimus can

be detected in prostate tumor tissue, as measured by a reduced level of immunostaining of phospho-S6 kinase. In a similar fashion, oral temsirolimus was tested in newly diagnosed prostate cancer patients who were about to undergo radical prostatectomy [Efstathiou *et al.* 2008]. Signs of successful target inhibition were also detected in these patients, although an associated increase in phospho-Akt and phospho-mTOR was seen. These results are consistent with other research suggesting that upstream Akt activation is observed with mTOR inhibition, which may be a mechanism of resistance [O'Reilly *et al.* 2006].

Everolimus has also been tested in CRPC [George *et al.* 2008]. Preliminary results from a phase II study demonstrated a 2.5 month time-to-progression (TTP) without any radiographic or PSA responses. Although these results were not encouraging, the majority of these patients were resistant to docetaxel-based chemotherapy. Given the potential for mTOR inhibitors as chemosensitizing agents [Grunwald *et al.* 2002], everolimus was also tested in combination with docetaxel in a phase I study using fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging as a pharmacodynamic endpoint [Ross *et al.* 2008b]. The combination was tolerable at doses of everolimus 10 mg daily with docetaxel 70 mg/m^2 every 3 weeks, with some evidence suggesting decreased FDG-avidity was associated with PSA declines.

IGF pathway

Non-androgen hormonal signaling with the IGF-1 receptor (IGF1R) appears to play an important role in the progression of CRPC. The IGF pathway regulates cell growth, protects cells from apoptosis, and promotes tumor cell invasion in a variety of human cancers. Thus, elimination of IGF1R signaling may produce a beneficial antitumor effect [Wu *et al.* 2005]. Some androgen-dependent cell lines increase IGF-1 and IGF1R expression when developing androgen-independent growth [Krueckl *et al.* 2004; Kiyama *et al.* 2003]. Therefore, targeting the IGF-1 axis may play an important role in the treatment of CRPC and trials with several agents are underway.

There are multiple ways to target the IGF-1 pathway using octreotide, small molecule tyrosine kinase inhibitors (TKIs) and receptor-binding antibodies. Somatostatin analogues, lantreotide [Maulard *et al.* 1995] and octreotide [Koutsilieris *et al.* 2004], that lower IGF-1 levels, have been tested in CRPC, and found to be associated with modest PSA responses. Lantreotide was associated with ≥50% PSA declines in 20% of CRPC patients [Maulard *et al.* 1995]. Octreotide in combination with dexamethasone was associated with ≥50% PSA declines in 60% of patients [Koutsilieris *et al.* 2004]. Further testing of somatostatin analogues is ongoing.

Small molecule TKIs and receptor-binding antibodies may prove useful to inhibit IGF receptor activation. These are currently being tested in phase II clinical trials in prostate cancer. A phase I study of an IGF1RTKI, NDGA (mesonordihydroguaiaretic acid) was performed in prostate cancer patients with a rising PSA after definitive local therapy [Ryan *et al.* 2008] One of 11 patients experienced a ≥50% PSA decline, and several other patients had a prolongation of PSA doubling time.

Humanized monoclonal antibodies specific to IGF-1R which inactivate the receptor, recently have entered clinical trials. Single-agent activity has been observed with IGF-1R blockade in patients with Ewing's sarcoma. Two humanized monoclonal therapeutic antibodies against IGF-1R have entered clinical trials for patients with prostate cancer: CP-751,871 and IMC-A12. A phase I combination trial of CP-751,871 with docetaxel demonstrated the tolerability of the regimen, and a randomized, phase II trial of docetaxel with or without CP-751,871 has been conducted, with results currently pending. The human monoclonal immunoglobulin (Ig) G1 (IgG1) antibody, IMC-A12, inhibits ligand-dependent receptor activation, and is currently being tested in prostate cancer [Rowinsky *et al.* 2007].

Initial data from preclinical studies targeting growth factor pathways (HER2, PI3K, mTOR and IGF) show that although we are able to hit the target, the modest activity found in the clinic is insufficient to justify further single-agent testing. Results of ongoing clinical trials using these agents in combination with chemotherapy or other synergizing agents are eagerly awaited.

Vascular endothelial growth factor and receptor

Plasma level of vascular endothelial growth factor (VEGF), a potent angiogenic growth factor, is an independent prognostic factor in men with metastatic CRPC and has been correlated with poor

prognosis and disease progression [George *et al.* 2001]. Anti-angiogenic therapies are hypothesized to be effective in preventing tumor-associated neo-angiogenesis. VEGF inhibition may also have an indirect antitumor effect when combined with chemotherapy through enhancement of permeability *via* vascular normalization [Jain *et al.* 2007]. Therefore, targeting of the VEGF pathway is a reasonable therapeutic approach for patients with prostate cancer. Initial attempts to target angiogenesis were performed with thalidomide [Figg *et al.* 2002]. Thalidomide and its analogs may inhibit angiogenesis and prostate tumor growth through multiple potential mechanisms, including inhibition of pro-angiogenic signals such as VEGF as well as immunomodulatory effects by affecting T-cell costimulatory activity [Teo, 2005; Bartlett *et al.* 2004]. A randomized phase II study of thalidomide in combination with docetaxel in CRPC demonstrated a 53% PSA decline (>50% decrease in PSA), and improved TTP and OS compared with docetaxel alone [Figg *et al.* 2001]. The study was underpowered to assess survival and toxicities of this combination included high rate of thrombosis, sedation, and neuropathy. Newer analogs of thalidomide (eg Lenalidomide—Revlimid®) with a safer toxicity profile are being investigated [Kalmadi and Raghavan, 2008].

Since angiogenesis is a clear target in prostate cancer, an alternative approach to inhibit angiogenesis by reducing binding of the ligand VEGF—the most potent driver—with the monoclonal antibody, bevacizumab. While single-agent trials failed to show an effect for bevacizumab [Figg *et al.* 2002], early studies in combination with docetaxel have been extremely promising. A phase II trial conducted by the CALGB combined bevacizumab with docetaxel and estramustine in men with CRPC and showed that 79% of patients had a greater than 50% PSA decrease, with a median TTP of 9.7 months, and OS of 21 months [Teo, 2005; Picus *et al.* 2003]. An additional phase II trial with bevacizumab in combination with docetaxel, prednisone, and thalidomide as first-line treatment in metastatic CRPC patients showed an encouraging 86% PSA response rate [Ning *et al.* 2006]. Low molecular weight heparin prophylaxis was required to prevent vascular events in this trial.

Based upon the promising results of the CALGB phase II trial [Picus *et al.* 2003], a randomized, double-blind, placebo-controlled phase III trial has been completed which compared docetaxel, prednisone and either bevacizumab or placebo every 3 weeks (CALGB 90401). The primary endpoint for this trial is OS, and accrual of 1020 patients is now complete with results being eagerly awaited.

Other drugs in development targeting angiogenesis are: aflibercept, sunitinib and sorafenib. Aflibercept (VEGF Trap) is a recombinantly produced fusion protein consisting of human VEGF receptor extracellular domains fused to the Fc portion of human IgG1. Aflibercept is a potent inhibitor of VEGF-A and VEGF-B and the whole VEGF family by inactivating these circulating factors [Verheul *et al.* 2007]. A phase III, randomized, double-blind, placebo-controlled trial is underway for patients with metastatic CRPC.

Evaluation of TKIs, which inhibit angiogenic growth factor receptor signaling in advanced prostate cancer, has recently begun. Sorafenib, sunitinib and vatalanib have been tested in CRPC. Sorafenib is an oral TKI that inhibits RAF kinase, VEGF receptor tyrosine kinase, and the platelet-derived growth factor (PDGF) receptor, and is currently approved for metastatic renal cell carcinoma [Bellmunt *et al.* 2009b; Escudier *et al.* 2009; Dahut *et al.* 2008]. A phase II study of 22 patients evaluated the activity of sorafenib in CRPC [Wu *et al.* 2006]. Of 19 patients who progressed, 10 progressed by PSA only and two patients with PSA progression were found to have significant improvement of bony disease. Similarly, in another report, 10 of 16 patients who discontinued sorafenib and did not receive any immediate therapy, demonstrated postdiscontinuation PSA declines of 7–52% [Chi *et al.* 2008a]. This raises the serious limitations that exist with these novel agents when PSA is used as an indicator of response and progression.

A phase II study investigating sunitinib in patients with metastatic CRPC has been performed [Periman *et al.* 2008]. All patients had received one or two prior chemotherapies, including docetaxel. At least 12 weeks without clinical progression was noted in 78.9% of patients. However, 47% of patients discontinued therapy because of toxicity, and two early deaths were seen. A phase III study has been initiated that will randomize patients with CRPC progressing after docetaxel to receive either sunitinib

or placebo in a 2 : 1 fashion. The primary endpoint is OS, and a planned 819 patients are to be enrolled.

Vatalinib (PTK787/ZK 222584) is another multi-targeted TKI inhibiting VEGFR 1–3 and PDGFR at nanomolar concentrations [Yano *et al.* 2000]. A small phase I study to evaluate preliminary efficacy in metastatic CRPC patients has been performed. Overall, one out of 19 patients demonstrated ≥50% reduction from baseline in serum PSA level and duration of response of 12 months; two other patients demonstrated ≥40% reductions in PSA with duration of 4 and 5 months, respectively [Armstrong and George, 2008].

As has been shown with other tumor types, targeting anti-angiogenic pathways in combination with chemotherapy with agents like bevacizumab, is one of the most attractive targets in prostate cancer. The results of the already completed CALGB 90401 trial will shed light on the role of angiogenesis inhibitors in CRPC.

Immunotherapy and vaccines

There are multiple characteristics of prostate cancer that make immune-based therapy a promising approach. Prostate cancer grows relatively slowly, which may allow the immune system, when stimulated, the necessary time to generate an antitumor immune response [Harzstark and Small, 2009]. Recent evidence has also suggested that prostate cancer is more immunogenic than expected, with the ability to induce spontaneous auto-antibodies in patients [Wang *et al.* 2005].

Immunotherapy, both active (eg vaccines) and passive (eg antibodies) for prostate cancer is currently being investigated with promising results.

Although PSA modulation is not a universally accepted marker of response, some data suggest the possibility that granulocyte-macrophage colony stimulating factor (GM-CSF) may have biologic and antitumor effects based on findings of PSA decline [Small *et al.* 1999]. Generally, low doses of GM-CSF are associated with greater stimulation of the immune response, whereas higher doses are not associated with additional stimulation of the immune response [Small *et al.* 2007a]. Some current vaccine approaches have been using GM-CSF as an adjunct in order to improve antigen presentation.

Two types of active immunotherapies have been developed in phase III trials. These include the autologous, dendritic cell-based immunotherapy and allogeneic whole cell-based immunotherapy. Dendritic cells are antigen-presenting cells processing and presenting antigens to T cells to illicit a specific immune response. This is possible *via* major histocompatibility complex (MHC) class I and class II molecules. APC 8015 (sipuleucel-T, Provenge) is an example of dendritic cell-based therapy. Sipuleucel-T is a vaccine that consists of autologous dendritic cells that have been pulsed *ex vivo* with a prostatic acid phosphatase (PAP)-GM-CSF fusion protein. Antigen presenting cells (APC) are isolated from the leukopheresis product at a central facility and cultured with a fusion protein that consists of PAP linked to GM-CSF, resulting in activation of the APCs and loading and processing of the PAP antigen for presentation to T cells. Phase I and II trials demonstrated the feasibility and safety of the approach, with evidence of immune responses to the fusion protein, and demonstrated antitumor effects [Small *et al.* 2000].

In an initial report of a phase III trial in asymptomatic metastatic CRPC, comparing sipuleucel-T to placebo, the primary endpoint of PFS was not met, but there was an improvement in OS (25.9 *versus* 21.4 months; $p = 0.02$) [Small *et al.* 2006; Simons and Sacks, 2006; Warren and Weiner, 2000]. These results have been recently confirmed in a multicenter phase III trial (IMPACT, D9902B trial) with final results of the 500 patient study recently presented at the 2009 American Urological Association annual meeting. The data confirmed a median survival advantage of 4.1 months for patients treated with sipuleucel-T compared to placebo (25.8 *versus* 21.7 months, respectively; HR: 0.775, $p = 0.032$). The US Food and Drug Administration is expected to review sipuleucel-T for possible approval in metastatic CRPC patients.

An alternative vaccine approach has been the use whole cells as an antigen source to provoke an immune response to multiple antigens. Whole tumor cells are used with GVAX® instead of PAP [Warren and Weiner, 2000]. It was developed using two human prostate cancer cell lines, LNCaP (derived from a prostate cancer metastasis to a lymph node in a patient with hormone-sensitive disease) and PC-3 (derived from a prostate cancer bone metastasis in a

patient with CRPC). The prostate cancer cells in these vaccines are genetically modified through adenoviral transfer to produce GM-CSF to induce APC growth, maturation, and induction. The cell lines are irradiated to prevent proliferation prior to patient administration [Warren and Weiner, 2000]. Two phase II trials demonstrated activity with one trial showing an OS of 26 months and another showing and expected OS data to be greater than 24.4 months [Higano *et al.* 2008; Small *et al.* 2007a].

Recently, two phase III studies evaluating GVAX® in comparison with, or in addition to, docetaxel-based chemotherapy in patients with metastatic CRPC have been conducted. In one study (VITAL-1), therapy with GVAX® was compared directly with docetaxel plus prednisone; accrual was completed, but the study was closed in October 2008 when a futility analysis revealed a <30% likelihood of the study meeting its primary endpoint of longer OS [Higano *et al.* 2009]. The second study (VITAL-2), which was initiated in 2005, was a phase III trial comparing GVAX® immunotherapy for prostate cancer in combination with docetaxel to docetaxel plus prednisone. The study was halted in August 2008 when an interim analysis revealed a higher number of deaths in the GVAX® arm. [Small *et al.* 2009b]. Several caveats could explain why the phase III failed when signs of activity were observed during initial studies. The trial design, allowing patients to receive steroids or concomitant chemotherapy could have prevented the development of active antibodies.

PROSTVAC® consists of constructs of fowlpox and vaccinia vectors and contains a triad of costimulatory molecule transgenes designated TRICOM™ (which include intercellular adhesion molecule B7.1, and leukocyte function associated antigen). In a randomized clinical trial, PROSTVAC® immunotherapy was associated with an 8.5-month improvement in median OS in men with metastatic CRPC without any detectable PSA response or improvement in PFS. These data provide evidence of prolonged antitumor activity, but need to be confirmed in a larger phase III study [Bellmunt *et al.* 2009c; Kantoff, 2009].

Another approach to immunotherapy taken for patients with CRPC has been through blockade of the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) costimulatory molecule expressed on the surface of T cells, although at the potential risk of breaking self tolerance and inducing autoimmunity as an adverse toxicity. Ipilimumab is a fully humanized monoclonal antibody against the cytotoxic CTLA-4 costimulatory molecule expressed on the surface of T cells. Blocking CTLA-4 signaling may enhance and maintain the activation and proliferation of tumor-specific T cells [Fong and Small, 2008], with potential consequent induction of tumor immunity. A single dose of ipilimumab at 3 mg/kg has been tested in a pilot trial in patients with CRPC [Small *et al.* 2007b]. Two out of 12 treated patients had a 50% PSA decline. Based on reported results of phase I and II trials, supporting radiotherapy as a potential immunosupportive maneuver to augment clinical responses to ipilumumab, a phase III trial of external beam radiation (XRT) to a bone metastatses, alone or with ipilumumab (the XRT to bone metastates is an attempt to focus this otherwise nonspecific immune stimulation), is underway [Slovin *et al.* 2009; Beer *et al.* 2008].

Extensive work has been done evaluating multiple immunotherapies for the treatment of prostate cancer and it has not been until recently when some positive results have emerged. However still much remains unknown about the best use of the immune based therapies in prostate cancer.

Apoptosis

Resistance to apoptosis is another mechanism attributed to treatment resistance and progression in prostate cancer. Bcl-2 overexpression, which is observed in a high percentage of patients with CRPC, has a critical role in the transition from androgen-dependent to androgen-independent tumor growth [Gleave *et al.* 1999]. Bcl-2 expression also contributes to resistance to docetaxel [Goodin *et al.* 2002].

A randomized phase II trial was conducted by the EORTC in patients with CRPC in an effort to enhance the efficacy of docetaxel in CRPC by combining the chemotherapeutic agent with oblimersen (an oligonucleotide antisense Bcl-2) [Sternberg *et al.* 2009b]. Chemotherapy-naive patients with PSA progression received oblimersen sodium administered before docetaxel *versus* docetaxel alone. Primary endpoints were confirmed PSA response and major toxic events. Confirmed PSA response was observed in 46% and 37% of 57 and 54 patients treated with

docetaxel and docetaxel–oblimersen, respectively. Partial response (RECIST) was achieved in 18% and 24%, respectively. Oblimersen added to docetaxel was associated with an increase in the incidence of grade 3 fatigue, mucositis, and thrombocytopenia. The primary endpoints of the study were not met by PSA response or toxicity.

One possible explanation for a lack of significant clinical benefit observed with oblimersen is that there are several prosurvival BCL-2 family members. The specific targeting of one member may simply be insufficient to overcome apoptotic resistance exerted by the other BCL-2 family members with preclinical testing supporting this hypothesis [Chi *et al.* 2009a]. More deep insight will be required for the future development of agents targeting the apoptotic pathways.

Chaperone proteins

Regulation of transcription is affected by histone acetylation status. Histone deacetylation is carried out by histone deacetylases. Inhibition of histone deacetylation, resulting in hyperacetylation, leads to transcriptional activation of repressed genes. Preclinical evaluation of histone deacetylase (HDAC) inhibitors has suggested the presence of significant antiprostate-cancer activity, although the mechanism of cancer cell death of these agents is not entirely elucidated.

The heat shock protein-90 (HSP90) has been shown to be critical for the proper folding and processing of the AR. The ability of HSP90 to bind to target proteins is dependent on its ability to bind and hydrolyze ATP. Inhibitors of the ATP hydrolase activity prevent Hsp90 from associating with its target proteins. The HSP90 molecular chaperone complex is essential for AR stability and maturation and thus has been identified as a potential therapeutic target for CRPC. A number of specific inhibitors have been developed against its ATPase activity. Small-molecule inhibitors of HDAC can also result in the loss of HSP90 ATP-binding activity through acetylation, with subsequent degradation of AR [Welsbie *et al.* 2009; Edwards *et al.* 2007]. *In vivo*, treatment of prostate cancer cells with an Hsp90 inhibitor, geldanamycin (a parent compound of 17-AAG), causes loss of AR activity, and degradation of AR protein [Smaletz *et al.* 2002]. Phase I trials have demonstrated the safety of 17-AAG in humans. A phase II study of 17-AAG in CRPC patients previously treated with chemotherapy unfortunately did not result in any patients achieving a 50% decline in PSA, and the median TTP was only 1.8 months [Heath *et al.* 2007]. Phase II studies of other HDAC inhibitors have also been conducted. Vorinostat (SAHA) has activity in preclinical models of prostate cancer [No authors listed., 2005]. Interestingly, there seems to be reduced activity of the compound in AR-negative prostate cancer cells, such as PC-3, and suppression of androgen signaling in the presence of the androgen receptor may sensitize prostate cancer cells to vorinostat [Marrocco *et al.* 2007]. However, a phase II study of vorinostat alone in patients previously treated with docetaxel chemotherapy did not demonstrate significant anticancer activity [Bradley *et al.* 2008]. Vorinostat is being tested in androgen-dependent prostate cancer in combination with androgen deprivation, based on the preclinical data suggesting that androgen deprivation may potentiate the actions of HDAC inhibition [Rokhlin *et al.* 2006].

Another chaperone protein of interest is clusterin. In cancer, clusterin has been largely defined in its role of inhibiting apoptosis. Clusterin is activated after therapeutic stress, functioning as a cytoprotective chaperone [Humphreys *et al.* 1999]. Clusterin's ability to inhibit apoptosis has also been shown to act through inhibition of activated BAX, a critical pro-apoptotic BCL-2 family member [Zhang *et al.* 2005]. Clusterin is overexpressed in a variety of human cancers, including prostate, and its expression increases with castration-resistant disease [July *et al.* 2002].

OGX-011 is a second-generation antisense oligonucleotide targeting human clusterin. Preclinical studies have indicated that clusterin suppresses apoptotic cell death in response to androgen withdrawal, chemotherapy and radiation [Zellweger *et al.* 2002; Miyake *et al.* 2000a, 2000b]. Phase I trials have established that OGX-011 can inhibit clusterin expression in PCa tissues in humans, and standard doses of chemotherapy can be delivered with OGX-011 at biologically active doses [Chi *et al.* 2008b, 2005]. A randomized phase II trial of OGX-011 with mitoxantrone or docetaxel in patients with CRPC who progressed to docetaxel demonstrated interesting antitumour activity [Saad *et al.* 2008]. In patients treated with mitoxantrone plus OGX-011, 27% had a PSA decline $\geq$50% from baseline, with a median OS of 11.4 months. In the docetaxel arm, 40% had a 50% decline in PSA with a median OS of 14.7 months,

of interest considering that those were previously progressing patients.

Another phase II study with OGX-011 randomized 82 patients with chemotherapy-naïve metastatic CRPC to receive first-line docetaxel with or without OGX-011 [Chi *et al.* 2009b]. PSA response rate (58% and 54%, respectively) and declines were similar. PFS for Arms A (with docetaxel) and B (without) was 7.3 (5.3–8.8) and 6.1 months (3.7–8.6). Median OS was 27.5 (19.2–∞) *versus* 16.9 months (12.7–26.0) [unadjusted HR = 0.60 (0.34–1.06), $p = 0.07$]. A phase III trial is being planned comparing docetaxel plus OGX-011 *versus* docetaxel in patients with metastatic CPRC, with a primary endpoint of OS. Follow-up of these agents is required to define their role in combination with chemotherapy in CRPC patients.

Bone targeting

Given the predilection of prostate cancer to metastasize to bone, agents capable of interrupting the interaction with bone are attractive for study. Clinical studies are developing agents that may alter tumor and bone interactions, including bisphosphonates, endothelin receptor antagonists, rank-ligand inhibitors, src kinase inhibitors and bone-targeted radiopharmaceuticals [Bradley *et al.* 2007]. Bisphosphonates, which inhibit the bone resorbing activity of osteoclasts by binding to the mineralized bone surface, are already an established treatment for patients with metastatic CRPC, and studies continue to define their use for earlier disease. Additional agents targeting bone–tumor interaction are also under clinical development.

RANK ligand

The interrelationship between osteoprotegerin (OPG), receptor activator of nuclear factor κ B (RANK) and its ligand (RANK-L) have been identified and their role is now well understood in the pathogenesis of bone metastasis in prostate cancer [Chen *et al.* 2006; Hofbauer and Schoppet, 2004; Brown *et al.* 2001]. Denosumab is a fully humanized monoclonal antibody specifically directed against RANK-L. It has proved to be effective in reducing bone resorption and increasing bone density in patients with physiologic and treatment-related bone loss [Bone *et al.* 2008; Ellis *et al.* 2008]. Its role in patients with bone-metastatic CRPC is now ready to be developed based on the results of the ongoing trials. Recent reports have suggested a similar effect in reducing skeletal-related events as zoledronic acid and its role in bone protection in men receiving ADT for prostate cancer has been recently demonstrated [Smith *et al.* 2009].

Endothelin-1 inhibitors

Endothelins are modulators of vasomotor tone, nociception, cell proliferation and angiogenesis but later identified as being elevated in men with prostate cancer and osteoblastic metastasis [Nelson *et al.* 1995]. Endothelin-1 (ET-1) is expressed in the prostate epithelium [Nelson *et al.* 1996]. Patients with metastatic prostate cancer have elevated levels of plasma ET-1 compared with patients with organ-confined cancer [Lassi and Dawson, 2009; Nelson *et al.* 1996, 1995]. ET-1 preferentially binds to ET-A receptor where, in addition to mediating a vasoconstriction response, ET-A signaling has been associated with proliferation, anti-apoptotic effects, and pain. ET-B, a second receptor functions as a decoy receptor and clearance mechanism for ET-1, thus mitigating its effects. ET-1 production by metastatic prostate cells in bone has been shown to be stimulated by osteoblasts, which are in turn stimulated by ET-1 to proliferate, stimulating new bone formation and osteoblastic metastases, contributing to a vicious cycle of progression [Carducci *et al.* 2002].

The more extensively tested compound is atrasentan. Atrasentan is predominantly an endothelin-A receptor antagonist. In a phase II, randomized, double-blind trial on 288 patients with asymptomatic metastatic CRPC, received either placebo or once-daily atrasentan, 2.5 or 10 mg [Carducci *et al.* 2003]. The 10 mg atrasentan group had a longer median TTP in intent-to-treat (187 *versus* 137 days for the placebo group, $p = 0.02$). Median time to PSA progression was 155 days for the atresantan 10 mg group compared with 71 days for the placebo group ($p = 0.002$). Encouraging results from this trial led to a phase III multicenter trial, in which 809 men with asymptomatic metastatic CRPC were randomized to atrasentan 10 mg daily *versus* placebo [Carducci *et al.* 2007]. The primary endpoints were TTP assessed radiographically and clinically. Atrasentan, disappointingly, did not reduce TTP relative to the placebo arm (HR 0.89, $p = 0.136$). In an exploratory analysis, however, bone alkaline phosphatase and PSA levels were significantly lower in the atrasentan arm ($p < 0.05$).

In a second phase III trial, 941 men with non-metastatic PSA-only CRPC were randomized to receive atrasentan 10 mg daily *versus* placebo [Nelson *et al.* 2008]. Fewer men treated with atrasentan (227) experienced disease progression compared with placebo (267), and the median survival was longer for the atrasentan group ($p = 0.176$); however, again it was not statistically significant. PSA doubling time prolongation and a decrease in alkaline phosphatase were also seen in the treatment group ($p = 0.031$ and $p = 0.001$, respectively) [Lassi and Dawson, 2009]. Although atrasentan did not meet the primary endpoint expectations, it did have an impact on molecular markers that indicate disease progression. A meta-analysis of pooled phase II and III data was able to show a significant increase in time to disease progression and in time to bone pain for patients taking atrasentan [Carducci *et al.* 2003]. Because of failure to demonstrate a perceived clinically relevant benefit, atrasentan has not yet obtained FDA approval. In combination with chemotherapy, an ongoing phase III trial involving 930 patients with metastatic CRPC with primary endpoint of OS is being conducted by the Southwest Oncology Group (SWOG) comparing docetaxel and prednisone *versus* docetaxel, prednisone, and atrasentan.

ZD4054 is another selective ET-A receptor antagonist. In a phase II trial on men with CRPC and bone metastases, 308 symptomatic patients were randomized to two doses of ZD4054, 15 or 10 mg once daily, or placebo. No improvement in TTP was seen; however, an interim analysis revealed an improvement in OS (23.5, 24.5 *versus* 17.3 months for placebo) [James *et al.* 2008]. Side-effect profiles were similar to atrasentan. On the basis of these encouraging results, three phase III trials involving 2500 CRPC patients are currently being conducted.

Src family kinases

Src-related kinases, and their upstream cell surface receptors have been implicated in prostate cancer progression. Src signaling is important for normal functioning of osteoclasts and bone resorption as well as osteoblast proliferation and bone deposition, and they are further implicated in bone metastases progression [Fizazi, 2007]. Dasatinib was clinically developed for chronic myelogenous leukemia based on its activity against the BCR-ABL KIT. It was subsequently shown to have significant activity against Src family kinases, resulting in direct antitumour effects in preclinical models of prostate cancer [Nam *et al.* 2005].

Phase II trials using dasatinib in a twice-daily and once-daily dosing regimens have been carried out in prostate cancer patients [Saad, 2009]. Only one patient in each of trial had a PSA response of >50% decline; however, lesser declines were noted, and decreases in bone turnover markers (serum bone alkaline phosphatase and urinary N-telopeptide) were also observed, providing proof-of-principal activity data. A randomized phase III trial of docetaxel with or without dasatinib is now being conducted, with a primary endpoint of OS.

Radiopharmaceuticals

Prostate cancer often metastasizes to bone, so recent efforts have rediscovered the concept of bone-targeting strategies with radiopharmaceuticals. In addition to targeted agents mentioned above, radiopharmaceuticals are beginning to show promise in treating CRPC. Early studies of patients with metatastic CRPC suggest that chemotherapy administered with a dose of a bone-seeking radiopharmaceutical may be superior to chemotherapy alone. To build on this strategy and fully integrate a repetitively dosed bone-seeking radiopharmaceutical into a contemporary chemotherapy regimen, early studies with docetaxel and samarium-153 (153Sm) lexidronam have been conducted with responses seen in patients with taxane-resistant disease [Morris *et al.* 2009; Tu *et al.* 2009]. These studies suggest that radiopharmaceutical therapy in combination with docetaxel may have more activity than either alone. Consolidation strategies using radiopharmaceuticals after response or disease stabilization with docetaxel are also being explored [Fizazi *et al.* 2009]. With these improved bone-targeted treatments we can decrease the serious skeletal morbidities associated with metastatic prostate cancer and may in the future improve OS.

Conclusions

The growing availability of a plethora of new therapies targeting different pathway will revolutionize patient management strategies in CRPC patients. Today, men with CRPC have more clinical trial options than ever before, and many promising agents are in late-stage clinical testing. The hypothesis that CRPC frequently remains driven by a ligand-activated AR and that CRPC tissues exhibit substantial residual androgen

levels despite gonadotropin-releasing hormone therapy, has generated a lot of expectations with compounds such as abiraterone and MVD 3100. These new oral compounds coupled with promising recent findings in immunotherapy (like sipuleucel-T) and on agents targeting angiogenesis (while awaiting the final results of the CALGB trial) will surely impact the management of patients with CRPC in the near future. Meanwhile, other new promising agents await more mature development. With the increased understanding of the biology of this disease, further trial design should incorporate improved patient selection to enrich for patient populations who may be most likely to benefit from treatment.

Conflict of interest statement

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