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Novel targeted therapeutics for metastatic castration-resistant prostate cancer

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Abstract

Virtually all patients that succumb to prostate cancer die of metastatic castration-resistant disease. Although docetaxel is the standard of care for these patients and is associated with a modest prolongation of survival, there is an urgent need for novel treatment strategies for metastatic prostate cancer. In the last several years, great strides have been made in our understanding of the biological and molecular mechanisms driving prostate cancer growth and progression, and this has resulted in widespread clinical testing of numerous new targeted therapies. This review discusses some of the key therapeutic agents that have emerged for the treatment of metastatic castration-resistant prostate cancer in the last 5 years, with an emphasis on both molecular targets and clinical trial design. These agents include mammalian target of rapamycin (mTOR) pathway inhibitors, anti-angiogenic drugs, epidermal growth factor receptor (EGFR) inhibitors, insulin-like growth factor (IGF) pathway inhibitors, apoptosis-inducing drugs, endothelin receptor antagonists, receptor activator of nuclear factor κB (RANK) ligand inhibitors, vitamin D analogues, cytochrome P17 enzyme inhibitors, androgen receptor modulators, epigenetic therapies, vaccine therapies, and cytotoxic T lymphocyte-associated antigen (CTLA)-4 blocking agents.

Keywords

Metastatic castration-resistant prostate; cancer; Targeted therapies; Immune therapies; Molecular targets; Clinical trials; Drug development

1. Introduction

Prostate cancer is the most common malignancy in men worldwide. In the United States, there were an estimated 186,300 new diagnoses of prostate cancer and 28,700 prostate cancer deaths in 2008, representing 25% of new cancer cases and 10% of male cancer deaths

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Conflict of interest

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[1]. This makes prostate cancer the second leading cause of cancer death in men. While the disease can potentially be cured when localized, metastatic prostate cancer remains incurable.

Treatment of localized prostate cancer is usually centered around surgery and/or radiation therapy. However, even after definitive local therapy, approximately 30–50% of patients will have a local or distant recurrence [2,3]. Patients with metastatic prostate cancer have a median survival of 3–7 years, and most men die of it [2]. Treatment for metastatic disease involves surgical castration or hormonal manipulation using gonadotropin-releasing hormone (GnRH) agonists, antiandrogens, or both. Although the majority of these patients initially respond to androgen deprivation therapy, all eventually progress to a state of castration-resistant prostate cancer (CRPC). Treatment options for these men are limited. Secondary hormonal manipulations, such as ketoconazole, are often used but these produce short-lived responses and do not improve survival [4]. Other acceptable approaches in these men include watchful waiting until the development of symptoms, or the initiation of cytotoxic chemotherapy. In this regard, the chemotherapeutic agent docetaxel has been shown to improve overall survival in patients with CRPC, but only by a median of 2.9 months (median survival 19.2 months versus 16.3 months using mitoxantrone, $P = .004$) [5,6]. Novel therapies for this patient population are urgently needed.

Since the approval of docetaxel by the Food and Drug Administration (FDA) in 2004, no new anti-cancer therapies have entered the market for the treatment of metastatic CRPC. On the other hand, the number of agents for CRPC in various stages of clinical development is higher than ever before. This has been made possible due to our accelerated understanding of the biological and molecular mechanisms underpinning prostate cancer growth and spread, which has fueled an expansion in research on new therapeutic approaches. This review will highlight novel targeted therapies that have emerged for CRPC in the last 5 years, focusing on the mechanism of action and developmental status of some key clinical compounds that have reached phase II and III clinical trials (Table 1). Advances in chemotherapeutic drugs, hormonal agents, and bisphosphonates will not be discussed herein.

2. Targeted treatments

Although a prostate cancer stem cell has yet to be conclusively demonstrated, prostate cancer clearly progresses from an androgen-dependent tumor (with features similar to the luminal differentiated glands of the prostate) to a castration-resistant tumor that has features of adult stem cells, including anti-apoptotic mechanisms, chemotherapy resistance, and reliance on nonhormonal signaling pathways [7]. Candidate prostate cancer progression pathways under investigation include epidermal growth factor receptor (EGFR) signaling, vascular endothelial growth factor (VEGF) receptor-mediated pathways, phosphatidylinositol 3-kinase (PI3K)/Akt signaling, the insulin-like growth factor (IGF) axis, Hedgehog signaling, mitogen-activated protein (MAP) kinase signaling, the endothelin axis, and others. Given the molecular complexity of these pathways in the prostate cancer cell and the potential redundancy of individual pathways in the process of cancer progression, the simultaneous inhibition of multiple pathways remains a common strategy to induce sustained and clinically meaningful responses in metastatic CRPC.

The major biologic processes under therapeutic investigation in CRPC involve growth and survival, nutrition, apoptosis, chemotherapy and hormone therapy resistance, extra-gonadal androgen production, modulation of the androgen receptor, angiogenesis, the bone interface, epigenetic regulation, immune surveillance and escape, and stem cell renewal. This article provides an overview of these pathways as they pertain to prostate cancer rational targets and the approaches that are currently being developed for therapeutic purposes (Table 1).

2.1. PI3K/Akt/mTOR pathway

In advanced prostate cancer, loss of the tumor suppressor gene PTEN occurs in more than 50% of metastatic lesions and in approximately 20% of locally advanced lesions [8,9]. Loss of PTEN correlates with high Gleason score and stage, chemotherapy resistance, and other features of advanced prostate cancers [8]. PTEN is a negative regulator of the phosphatidylinositol 3-kinase (PI3K)/Akt survival pathway, and advanced prostate cancers frequently have elevated levels of phosphorylated (activated) Akt [10]. The Akt pathway is involved in signal transduction from multiple cell surface receptors, including the insulin receptor, epidermal growth factor receptor, insulin-like growth factor receptor, platelet-derived growth factor receptor, and interleukin-6 receptor, and it is likely to function as a cellular sensor for nutrient and growth signals [11]. In addition to promoting cell survival through the inhibition of apoptosis, the Akt pathway regulates cell growth, proliferation, and angiogenesis through the mTOR (mammalian target of rapamycin) pathway and the facilitated translation of signals such as c-Myc, cyclin D, and vascular endothelial growth factor [10]. Restoration of functional PTEN activity or inhibition of mTOR activity can block the growth of PTEN−/− prostate cancer xenografts in mice and restore chemotherapy (and possibly hormonal) sensitivity [12,13].

Rapamycin is a natural compound derived from soil samples containing the bacterium *Streptomyces hygroscopicus*, and has been used as a potent immunosuppressive agent in solid organ transplantation. Its antiproliferative properties and anti-tumor activity in cell lines also led to its clinical development in cardiology as a means of preventing stent restenosis and in oncology, in which a wide variety of tumors were found to exhibit sensitivity to this agent and its analogue, temsirolimus [14–16]. Temsirolimus has now been approved for the treatment of metastatic renal cell carcinoma [17]. Toxicities with rapamycin and its analogues are predictable and are not dose-related; they include maculopapular rash, hypertriglyceridemia, hyperglycemia, allergic reactions, pedal edema, mucositis, and thrombocytopenia [14,17–19].

Although mTOR inhibitors probably have little single-agent activity in advanced CRPC [20], the combination of these agents with docetaxel is an attractive option given their ability to reverse chemotherapy resistance in prostate cancer cell lines [21]. In addition, these agents induce apoptosis when they are given in combination with chemotherapy in patients who have demonstrable activation of the Akt pathway as a result of PTEN mutation/loss or other genetic alterations [22]. To this end, the mTOR inhibitor, everolimus, is currently being evaluated in combination with docetaxel for the first-line treatment of metastatic CRPC in a phase I/II clinical trial [23]. Everolimus is already approved for the treatment of advanced renal cell carcinoma [24]. A new mTOR inhibitor, deforolimus (AP23573), is also

being investigated in the phase II setting as single-agent therapy for men with advanced taxanerefractory CRPC.

2.2. Angiogenesis targets

Tumor angiogenesis is likely to be an important biologic component of prostate cancer metastasis, and elevated levels of the potent angiogenic molecule, vascular endothelial growth factor (VEGF), have been shown to correlate with advanced clinical stage and survival [25,26]. In a retrospective study of archived serum samples, VEGF levels were independently associated with survival from prostate cancer [27]. Similarly, antibodies to VEGF have slowed prostate xenograft growth rates, especially in combination with chemotherapy [28,29].

These findings led to the phase II CALGB 90006 trial, which added bevacizumab to docetaxel and estramustine in men with metastatic CRPC. Among 79 treated patients in this study, a fall in PSA of 50% or more was seen in 65% of men, median time to progression was 9.7 months, and overall median survival was 21 months [30]. Other phase II trials combining docetaxel and bevacizumab have also shown promising results [31,32]. These favorable trials have led to the design of a phase III randomized study (CALGB 90401) evaluating docetaxel 75 mg/m^2 every 3 weeks and prednisone 10 mg daily plus either bevacizumab 15 mg/kg or placebo given every 3 weeks. The primary endpoint of this trial is overall survival, and accrual of 1020 patients with metastatic CRPC has been completed. The initial results of this pivotal trial are awaited.

Thalidomide was originally developed in the 1960s for treatment of morning sickness and subsequently linked to teratogenic effects resulting in phocomelia and dysmelia. Whereas the exact mechanism of teratogenesis is unproven, the metabolites of thalidomide have been shown to inhibit angiogenesis through multiple potential mechanisms, including inhibition of pro-angiogenic signals such as VEGF, basic fibroblast growth factor (bFGF), interleukin-6, and tumor necrosis factor-α [33,34]. Preclinical studies suggest that thalidomide also has T-cell co-stimulatory activity and immunomodulatory properties. Phase I/II studies using high doses of thalidomide as a single agent have yielded low PSA response rates in the order of 20% [33,35]. However, in a randomized phase II trial of weekly docetaxel and low-dose thalidomide versus docetaxel alone, PSA responses, time to disease progression, and overall survival were greater in the combination arm [36]. Although this trial was underpowered to detect a difference from the standard arm, the clinical activity and manageable toxicity of this agent have led to the development of more potent thalidomide analogues for combination therapy, and these are currently undergoing clinical evaluation. Finally, a recent report of a phase II trial using a three-drug combination of docetaxel, thalidomide and bevacizumab showed PSA responses in approximately 80% of patients; however neurotoxicity was significant with this combination [37].

Toxicities with thalidomide include deep venous thrombosis, sedation, neuropathy, constipation, and fatigue. Newer thalidomide analogues with immunomodulatory features have been developed that lack the neurotoxicity of thalidomide but retain many of the T-cell modulatory effects, anti-angiogenic properties, and even direct pro-apoptotic functions [34]. Lenalidomide and CC-4047 are second-generation compounds with much more potent

tumor necrosis factor-α inhibition than the parent compound, and clinical testing with these agents has begun. For example, several phase I and II studies have revealed PSA responses and partial radiological responses with lenalidomide, both when used alone and when combined with ketoconazole or docetaxel [38–40]. However, phase III trials using thalidomide or lenalidomide in CRPC have not yet been conducted.

There has been a recent interest in the evaluation of tyrosine kinase inhibitors (TKIs), agents which block angiogenic growth factor targets such as the VEGF and PDGF receptors. The drug sorafenib is an oral inhibitor of RAF kinase, VEGFR, and PDGFR, which has been approved for use in metastatic renal cell carcinoma and hepatocellular carcinoma [41,42]. In phase II studies using sorafenib in men with metastatic CRPC, this agent was shown to prevent radiological progression and cause regression of bone metastases in some patients, but without affecting PSA levels [43,44]. The agent sunitinib and a novel multi-kinase inhibitor, vatalinib, are currently being tested in phase II studies in combination with docetaxel for chemotherapy-naïve CRPC; radiological responses rather than PSA responses have been chosen as primary endpoints in these trials. Finally, single-agent sunitinib is being evaluated in a phase III study of patients with docetaxel-refractory disease.

An alternative anti-angiogenic strategy is the use of VEGF decoy receptors (VEGF-Trap) to saturate circulating VEGF and prevent it from binding to its natural transmembrane receptor. One such agent is aflibercept (AVE0005), a novel recombinant decoy fusion protein of VEGFR and the Fc fragment of IgG1 [45]. In a phase I/II study of intravenous aflibercept combined with docetaxel in 54 heavily-pretreated patients with advanced solid tumors, the optimal dose of aflibercept was determined to be 6 mg/kg given every 3 weeks [46]. Toxicities from this combination regimen included neutropenia, hypertension, proteinuria, epistaxis, and dysphonia. Five patients (9%) achieved partial radiological responses, and 32 (59%) had stable disease. A multicenter, randomized, placebo-controlled phase III study of docetaxel with or without aflibercept in men with chemotherapy-naïve metastatic CRPC is now accruing patients.

A final approach to angiogenesis inhibition involves the use of tumor-vascular disrupting agents, drugs that primarily act against established tumor blood vessels by disrupting vascular endothelial cells and causing a range of subsequent antivascular effects [47]. The prototype in this class of agents is 5,6-dimethylxanthenoine-4-acetic acid (DMXAA). Motivated by experiments showing that DMXAA functioned synergistically with docetaxel in human prostate cancer xenografts [48], a multicenter randomized phase II trial of docetaxel plus or minus DMXAA (1200 mg/m^2 intravenously every 3 weeks) was conducted for men with metastatic CRPC in the first-line setting. In that study of 71 patients, PSA responses (>30% PSA reduction) at 3 months were 47% and 63% in the docetaxel-alone and docetaxel-DMXAA arms, respectively, and radiological response rates were 9% and 23% in the monotherapy-arm and the combination-arm, respectively [49]. Adverse events with DMXAA-docetaxel included neutropenia/febrile neutropenia, cardiac toxicities (supraventricular tachycardia, myocardial ischemia), gastrointestinal effects, and infectious complications.

2.3. EGFR and PDGFR pathways

The rapid development in the last several years of small molecules that inhibit tyrosine kinases has yielded encouraging results in a host of cancers. Demonstration of tumor response has sometimes correlated with mutation in the target tyrosine kinase, such as epidermal growth factor receptor (EGFR), Bcr-Abl, and c-Kit. In these cases, the target mutation has played a central role in the pathogenesis of these tumors. In prostate cancer, no such mutations have been identified, perhaps explaining why early trials of tyrosine kinase inhibitors in prostate cancer have been disappointing.

EGFR is overexpressed in 40–80% of prostate cancer cells, and over-expression may be more common in African American men with prostate cancer [50]. Furthermore, preclinical data suggested a correlation of EGFR expression with Gleason sum and androgen independence [51]. In phase II studies of approximately 100 patients with castration-resistant disease evaluating the EGFR tyrosine kinase inhibitor gefitinib, minimal activity and no PSA responses were reported [52,53]. Gefitinib resistance may be related to overactivity of the PI3K/Akt pathway in prostate cancer, and thus combinations of agents that target multiple pathways may be more beneficial [54]. In an effort to overcome this resistance, trials combining EGFR or dual kinase inhibitors with other novel agents are in development. For example, gefitinib is currently being tested in combination with the Akt/mTOR inhibitor, everolimus, in a phase II trial as first-line therapy for metastatic CRPC.

Prostate cancer cells express high levels of platelet-derived growth factor receptor (PDGFR), and signaling through this mechanism converges with the PI3K/Akt pathway which has been implicated in prostate cancer progression. Single-agent activity with the PDGFR inhibitor imatinib has been disappointing [55]; however, encouraging results in combination with weekly docetaxel have been reported in the phase I setting [56]. A phase II randomized trial of this combination compared with docetaxel alone is in progress, but early results from this study suggested a lack of improvement in median progression-free survival in men receiving docetaxel plus imatinib [57]. Plans to move forward with imatinib as a potential therapeutic agent for prostate cancer in the future are lacking.

Another potential target in this family of receptors is the HER2/neu tyrosine kinase, whose expression has been shown to increase androgen receptor activation leading to prostate cancer growth and survival [58]. However, phase II studies using the anti-HER2 monoclonal antibody trastuzumab showed minimal efficacy in CRPC, perhaps due to a low frequency of HER2 over-expression [59]. Studies using the dual EGFR/HER2 small molecule inhibitor lapatinib in asymptomatic CRPC are now being conducted, but early results have shown PSA responses in only about 10% of participants [60].

2.4. Apoptosis

Apoptosis is regulated by pro-apoptotic and anti-apoptotic proteins that are recruited as a result of apoptotic stimuli such as DNA damage, chemo- and hormonal therapy, and irradiation. Bcl-2, an anti-apoptotic factor, is an attractive molecular target in the treatment of CRPC. In human prostate carcinoma cell lines as well as in clinical prostate cancer specimens, increased Bcl-2 expression induces the transition to androgen-independent cell

growth [61], and confers resistance to many antineoplastic agents including taxanes [62]. These findings suggest that Bcl-2 over-expression may mediate clinical resistance to both androgen deprivation and chemotherapy in prostate cancer patients.

Oblimersen is a synthetic antisense oligonucleotide that hybridizes to *bcl-2* mRNA and inhibits Bcl-2 protein expression [63]. In mice bearing xenograft tumors from androgen-independent human prostate cancer cell lines, oblimersen markedly enhanced the anti-tumor activity of docetaxel resulting in increased rates of complete tumor regression compared with animals treated with docetaxel alone [64]. Because docetaxel itself partially inactivates the Bcl-2 protein (by phosphorylation), the addition of oblimersen to docetaxel is a rational therapeutic strategy. To this end, a phase I/II study using oblimersen (given by continuous intravenous infusion on days 1–8) with docetaxel (on day 6) every 3 weeks in patients with CRPC showed that 14/27 men (52%) achieved PSA responses while 4/12 men (33%) with measurable disease achieved partial radiological responses [65]. Adverse events with this combination were myelosuppression (including febrile neutropenia), alopecia, fatigue, diarrhea, and nausea/vomiting. Toxicities specifically attributed to oblimersen were fever (beginning 2–3 days after drug initiation), aspartate aminotransferase elevations, hypophosphatemia, and deep vein thrombosis. A randomized phase II trial evaluating docetaxel (given on day 5) with or without oblimersen (by continuous intravenous infusion on days 1–7) in patients with metastatic CRPC was recently reported. Discouragingly, this study revealed that PSA responses were similar in the docetaxel–oblimersen arm and in the docetaxel-alone arm (46% and 37%, respectively), and partial radiological responses were also similar (18% and 24%, respectively) [66]. In addition, docetaxel–oblimersen was associated with an increased incidence of grade 3–4 fatigue, mucositis, and thrombocytopenia; and caused more major toxic events (40.7% versus 22.8%, respectively).

AT-101 (R-gossypol acetate) is a polyphenolic compound derived from the cottonseed plant that inhibits the function of all Bcl-2 – related proteins (Bcl-2, Bcl-xL, Mcl-1, and Bcl-w) [67]. By blocking the binding of Bcl-2 family members with pro-apoptotic proteins and up-regulating specific pro-apoptotic factors, AT-101 lowers the threshold for cancer cells to undergo apoptosis [68]. Preclinically, AT-101 has shown anti-tumor activity in a variety of tumor types including prostate cancer [69]. A phase I/II study of oral AT-101 used alone was conducted in men with CRPC and no prior chemotherapy. In that study, the optimal dose was determined to be 20 mg/day for 21 out of 28 days, and common toxicities included diarrhea, fatigue, nausea, anorexia, and small bowel obstruction [70]. Two of 23 patients (9%) had a ≥50% PSA decline, but no patient achieved a radiological response. A second phase I/II study was performed by combining AT-101 (on days 1–3 of each cycle) with docetaxel (given every 3 weeks) in men with docetaxel-naïve CRPC. In that study, the optimal dose of AT-101 was found to be 40 mg twice daily on days 1–3 of each chemotherapy cycle, and adverse events of this combination included neutropenia, lymphopenia, fatigue, nausea, diarrhea, and hypophosphatemia [71]. Eight of nine patients treated at the optimal dose (89%) had a ≥50% PSA decline, and 2 of 6 patients with measurable disease (33%) had a partial radiologic response. A multicenter randomized phase II study evaluating docetaxel plus or minus oral AT-101 in the first-line treatment of metastatic CRPC is now underway.

2.5. IGF pathway

The insulin-like growth factor type-1 receptor (IGF-1R) and its ligands may also play a key role in prostate cancer carcinogenesis through mechanisms that involve mitogenesis, anti-apoptosis, and cellular transformation. Epidemiological studies have shown that increased circulating insulin-like growth factor type-1 (IGF-1) levels and decreased insulin-like growth factor binding protein-3 (IGFBP-3) levels are associated with higher risk of developing prostate cancer [72]. Conversely, partial inactivation of the IGF-1R seems well tolerated and may protect individuals from prostate cancer. In addition, IGF-1R is often overexpressed in prostate tumors and can mediate prostate cancer cell proliferation and resistance to androgen ablation therapy [73,74]. A promising strategy to inhibit the function of the IGF-1R is the use of monoclonal antibodies that bind to the extracellular domain of this transmembrane receptor [75]. In prostate cancer cell lines as well as in xenograft models, such antibodies can inhibit growth of both androgen-dependent and -independent tumors [76,77].

IMC-A12 (cixutumumab) is a fully human IgG1 monoclonal antibody that specifically targets the IGF-1R, inhibiting ligand binding and IGF signaling [78]. A phase II study of intravenous IMC-A12 (10 mg/kg every 2 weeks) used as monotherapy in men with asymptomatic metastatic CRPC was recently reported. In that study, 9 of 31 patients (29%) demonstrated lack of radiographic progression after 6 months of treatment, and an even greater number had PSA responses [79]. Adverse events related to this agent were fatigue, hyperglycemia (usually asymptomatic), thrombocytopenia, hyperkalemia, and pneumonia. A phase II study combining IMC-A12 (6 mg/kg on days 1, 8, and 15 of a 3-week cycle) with mitoxantrone in the second-line treatment of docetaxel-refractory metastatic CRPC is currently underway.

CP-751,871 (figitumumab) is the second fully human anti-IGF-1R IgG2 monoclonal antibody to enter clinical trials [80]. A phase I study of intravenous CP-751,871 given in combination with docetaxel to men with metastatic CRPC has been completed. In that study, 4 of 18 patients (22%) had a radiographic partial response to therapy, and an additional 2 men (11%) had disease stabilization for >6 months [81]. Toxicities of this combination regimen were neutropenia (including neutropenic fever), diarrhea, and transient hyperglycemia. A phase II study of CP-751,871 (20 mg/kg on day 1 of a 21-day cycle) combined with docetaxel in men with chemotherapy-naïve (arm A) and docetaxel-resistant (arm B) CRPC is now open.

2.6. Bone interface

An emerging target with a prominent role in prostate cancer progression and development of bone metastases is endothelin-1, a peptide that also plays an important role in vascular tone [82]. Preclinical studies suggest that endothelin A receptors are overexpressed in prostate cancer, and higher tissue endothelin receptor levels in patients with prostate cancer correlate with advanced tumor stage, grade, and metastases [83]. Endothelin-1 is a potent vasoconstrictor, and antagonists have been developed for the treatment of pulmonary hypertension. In oncology, endothelin is likely to be involved in the paracrine signals between osteoblasts and prostate cancer cells that regulate the development of bone

metastases and have been shown to influence cell growth and proliferation, regulate osteoblast activity, and inhibit apoptosis [84–86]. These observations suggest that this pathway may be a rational target for the interference of tumor-stromal interactions.

Atrasentan is a highly selective endothelin A receptor antagonist and has been extensively tested in prostate cancer [87]. In phase II trials, a 10-mg dose of oral atrasentan was found to prolong time to progression compared with placebo in men with metastatic CRPC (196 versus 129 days, respectively; $P = .02$) [88]. Adverse events with atrasentan were mild and related to vasomotor reactions including headache, rhinitis, flushing, and peripheral edema. In addition, favorable effects were seen in markers of bone deposition and resorption. However, in a placebo-controlled double-blind phase III trial involving 809 patients with metastatic CRPC, atrasentan (10 mg/day) did not reduce the risk of disease progression ($P = .14$), despite evidence of biologic effects on PSA and bone alkaline phosphatase [89]. A second phase III trial in non-metastatic CRPC that randomized 467 men to atrasentan and 474 to placebo also failed to improve time to metastatic progression ($P = .29$) or overall survival [90]. A large cooperative group phase III clinical trial evaluating docetaxel with or without atrasentan as first-line therapy for metastatic CRPC is now underway. This study was fueled by promising results of early phase II trials evaluating this combination [91], and from preclinical data showing synergism between docetaxel and atrasentan *in vitro* and *in vivo* [92].

A novel small molecule endothelin receptor inhibitor, zibotentan (ZD4054), has shown initial promising results [93]. In a phase II trial of zibotentan versus placebo in men with metastatic CRPC, this agent did not improve time to disease progression (the primary study endpoint) ($P = .55$); however overall survival was longer on the zibotentan arm ($P = .01$) [94]. Although survival was a secondary endpoint in that trial, this has led to the design of several ongoing placebo-controlled phase III clinical studies evaluating zibotentan either alone or in combination with docetaxel in patients with metastatic CRPC. A further phase III trial is investigating single-agent zibotentan in men with non-metastatic castration-resistant disease.

2.7. RANK ligand inhibitors

Interactions between tumor cells and the bone marrow microenvironment have been postulated as an additional important mechanism in the pathogenesis of bone metastasis. Tumor-associated cytokines have been shown to induce the expression of RANKL (the receptor activator of nuclear factor κB ligand), which binds and activates RANK which is found in osteoclasts [95]. Inhibition of the RANKL system has recently been the focus of much research and represents an evolving bone-targeted strategy. Among the approaches employed are monoclonal antibodies to RANKL and the use of recombinant osteoprotegerin (the natural decoy receptor of RANKL), both of which significantly inhibit osteoclastic function *in vitro* and *in vivo* [96].

Denosumab, a fully human monoclonal antibody against RANKL, has entered clinical trials in prostate and breast cancers [97]. In a phase II randomized study evaluating 50 patients with metastatic prostate cancer, denosumab (180 mg subcutaneously every 4 weeks) produced a reduction in bone resorption over that of zoledronate as indicated by a lowering

of urinary N-telopeptide levels, and also resulted in less skeletal-related events (SREs) [98]. A multi-center phase III double-blind study comparing denosumab with zoledronate in the prevention of SREs in patients with metastatic CRPC has recently completed accrual of 745 men.

2.8. Vitamin D analogues

Vitamin D derivatives may have differentiation, antiproliferation, and chemosensitizing properties in prostate cancer [99], and epidemiological studies have shown an increased risk of prostate cancer in those with relative vitamin D deficiency [100]. A phase II trial of weekly docetaxel and high-dose calcitriol demonstrated PSA responses in 30 of 37 patients (80%) and radiological responses in 8 of 15 (53%), with a median time to progression of 11.4 months and a median survival of 19.5 months [101]. A randomized study with a total of 250 patients (125 per arm) comparing this combination with docetaxel alone resulted in more than 50% decline of PSA level in 63% of the patients receiving the combination compared with 52% with docetaxel alone ($P = .07$). Interestingly, the authors reported a survival difference in favor of the combination arm (23.4 months versus 16.4 months; $P = 0.03$) [102].

These results led to the design of a large phase III placebo-controlled trial in metastatic CRPC evaluating docetaxel chemotherapy with or without calcitriol, powered to detect a survival benefit as the primary endpoint. However, early reports from this trial have shown that the primary endpoint was not met and that mortality was actually increased in the calcitriol arm, leading to premature closure of the study [103]. At the time of closure, over 900 of the planned 1200 patients had enrolled in the study. Full analysis of the clinical data in an effort to elucidate the cause of the higher mortality rate in the docetaxel–calcitriol arm is expected.

2.9. CYP17 system

It has recently been recognized that the androgen receptor (AR) and ligand-dependent AR signaling commonly remain active and upregulated even in men with castrate levels of testosterone (i.e. <50 ng/dl) [7]. Standard hormonal therapies inhibit gonadal androgenesis, but do not affect androgen synthesis from adrenal or other extragonadal sources that may account for 5–10% of total androgen production. It has also been suggested that CRPC itself may produce intratumoral androgens autonomously [104]. In addition, over-expression of CYP17 has been demonstrated in tumors of men with CRPC [105].

The novel agent, abiraterone acetate, is an oral selective inhibitor of the microsomal enzyme cytochrome P17 (17,20 lyase and 17α-hydroxylase) that is a key regulator of adrenal androgen synthesis. Phase I studies using abiraterone in men with CRPC (both pre- and post-docetaxel) have shown a substantial number of PSA responses and also some partial radiological responses in men with bony and visceral metastases [106,107]. In a phase II study of 33 chemotherapy-naïve ketoconazole-naïve patients with CRPC, PSA reductions of ≥50% were observed in 85% of men [108]. Another phase II trial in the docetaxel-pretreated population showed that 24 of 47 patients (51%) achieved ≥50% PSA reductions, and 6 of 35 evaluable men (17%) had a partial radiological response [109]. Impressively, in a further

phase II study of docetaxel-refractory patients, PSA declines of ≥50% were even seen in ketoconazole-pre-treated men (8/24 patients; 33%) [110]. Common side effects of this agent include hypokalemia, hypertension, and pedal edema. These effects are explained by a syndrome of secondary mineralocorticoid excess, which improves with use of the mineralocorticoid receptor antagonist, eplerenone [106]. A randomized phase III study of single-agent abiraterone compared to placebo in men with chemotherapy-naïve metastatic CRPC is now underway. Another phase III study of abiraterone versus placebo in docetaxel-refractory disease has recently completed accrual of 1158 patients [111], and preliminary results are eagerly awaited.

2.10. Androgen receptor modulation

The effects of androgen receptor (AR)-mediated prostate cancer growth are dependent upon the translocation of cytosolic ligand-activated AR into the nucleus with subsequent binding to transcriptional DNA elements. MDV-3100 is an oral small molecule androgen receptor modulator that binds to the AR with greater relative affinity than the commonly used antiandrogen bicalutamide, reduces the efficiency of its nuclear translocation, and impairs both DNA binding to androgen response elements and recruitment of transcriptional coactivators [112]. In preclinical studies, MDV-3100 was shown to induce significant tumor regression in mouse models of human CRPC [113].

A phase I/II study using MDV-3100 as monotherapy in chemotherapy-naïve as well as docetaxel-pretreated men with CRPC has recently been completed. In that study, PSA declines of >50% at 12 weeks were observed in 57% (37/65) of naïve and 45% (22/49) of post-chemotherapy patients, while radiographic control at 12 weeks was seen in 35/47 patients (74%) with soft tissue lesions and in 50/81 patients (62%) with bone lesions [112,114,115]. In addition, MDV-3100 had positive effects on two exploratory biomarker analyses: positron emission tomography (PET) imaging, and circulating prostate cancer tumor cell (CTC) analysis. Adverse events observed with this agent included fatigue, nausea, anorexia, and rash; seizures were reported in three patients [115]. A multinational, double-blind phase III trial is currently being planned and will randomize 1200 patients with docetaxel-refractory disease (2:1) to receive either MDV-3100 or placebo [116]; the primary endpoint of this study will be overall survival.

2.11. Epigenetic approaches

Histone deacetylases (HDACs) are critical regulators of histone acetylation status, which is critical for AR-mediated transcriptional activation of genes implicated in the regulation of cell survival, proliferation, differentiation and apoptosis [117]. Vorinostat is a potent oral HDAC inhibitor that has shown anti-tumor activity in prostate cancer cell lines and animal models [118]. This agent has been approved for the treatment of cutaneous T-cell lymphoma [119]. However, a phase II study of vorinostat in the second-line treatment of men with CRPC that had progressed on docetaxel did not show significant PSA or radiological responses and was associated with a high frequency of grade 3/4 adverse events which included fatigue, nausea, anorexia, vomiting, diarrhea, and weight loss [120]. A novel oral HDAC inhibitor, panobinostat (LBH589), is currently in phase I/II development as an

adjunct to docetaxel in first-line CRPC [121], and also as single-agent therapy in docetaxel-refractory disease.

DNA methylation of key tumor suppressor genes may represent a second important epigenetic mechanism by which prostate cancer progresses to a castration-resistant state [122]. Azacitidine, an agent approved for the treatment of myelodysplastic syndromes [123], appears to exert its antineoplastic effects by inhibiting DNA methyltransferases (DNMTs) in promoter regions of genes, leading to reversal of gene silencing [124]. In preclinical cellular and animal models, azacitidine was found to reverse resistance of prostate cancer to androgen deprivation therapy and chemotherapy [125], making this agent an attractive choice for clinical trial development. As such, a single-arm phase II study of azacitidine (75 mg/m^2 subcutaneously for 5 days every 28 days) given to 36 patients with chemotherapy-naïve CRPC resulted in a fall in PSA doubling time in 65% of patients and produced a median progression-free survival of 12.6 weeks [126]. Significant toxicities of this agent included fatigue and neutropenia. Another phase II study evaluating the combination of docetaxel and azacitidine in men with metastatic docetaxel-pretreated CRPC is now underway.

3. Immunotherapy

Entraining the immune system to overcome tumor-induced tolerance is the goal of nearly every cancer vaccine program, and active immunotherapy with vaccination against tumor antigens has been pursued in many different cancer models. A variety of approaches have been employed including: dendritic cell-based therapies; novel adjuvants such as Bacille Calmette-Guérin (BCG), granulocyte-monocyte colony-stimulating factor (GM-CSF), and viral carriers; single-antigen or whole cell vaccines; and genetically modified tumors. More recently, combination therapies using co-stimulatory molecules, CTLA-4 blockade, toll-like receptor agonism, and intracellular viral or bacterial mediators have been developed [127–130].

Although prostate cancer has not traditionally been thought of as a disease amenable to immunotherapeutic approaches, this notion has recently been reconsidered. Prostate cancer is a slow-growing disease, which may allow a stimulated immune system the necessary time to generate an anti-tumor response [131]. Furthermore, recent evidence suggests that prostate cancer is more immunogenic that previously thought, with the ability to induce spontaneous autoantibodies [132]. For these reasons, and because of lower anticipated toxicities with immune-based therapies, there are currently a number of immunological strategies under clinical development. Those that have generated the most recent interest include the sipuleucel-T (Provenge®) autologous prostatic acid phosphatase (PAP)-loaded dendritic cell vaccine, the GVAX® allogeneic recombinant whole cell vaccine, and cytotoxic T lymphocyte-associated antigen (CTLA)-4 inhibitory approaches. Other immune-based strategies for advanced prostate cancer have been reviewed elsewhere [130,133]. Each of these modalities is designed to stimulate the immune system to recognize a previously tolerogenic tumor in a cancer-specific way.

3.1. Sipuleucel-T

Sipuleucel-T (Provenge®) is a vaccine derived from CD54 + dendritic cells, the major antigen-presenting cells, which are apheresed from individuals and processed with the recombinant fusion protein PAP (prostatic acid phosphatase) and GM-CSF. PAP was chosen on the basis of its prostate cell membrane localization and the success of preclinical models using it to generate prostate-specific immune responses and autoimmune prostatitis [134]. Minimal activity has been reported in phase II trials in patients with CRPC. In a randomized phase II/III trial comparing sipuleucel-T against placebo in 127 asymptomatic men with metastatic CRPC (PAP positive), the investigators reported no significant differences in time to disease and pain progression ($P = .052$), which corresponded to the primary study endpoint [135]. Patients randomized to placebo were crossed over to receive the active vaccine at the time of progression, whereas those initially randomized to receive the active vaccine were treated at their physician's discretion at the time of progression. This post-progression management period was not part of the initial study protocol and was not prospectively controlled. Whereas the study as designed was negative, a 3-year exploratory update suggested a significant improvement in survival for those randomly assigned to the active vaccine ($P = .01$). It is highly probable that survival differences were due to post-vaccine treatments. Post hoc analyses also suggested that the benefits of sipuleucel-T may have been limited to the subgroup of men with tumor Gleason sums of 7 or lower. Although preparation and production of large-scale quantities of individually tailored vaccine can be challenging, this vaccine was well tolerated; minimal infusion-related fevers and tremors/rigors were the predominant adverse events [135].

A second phase II/III trial that randomized 98 men with asymptomatic CRPC to either sipuleucel-T or placebo also failed to show a statistically significant improvement in time to progression (the primary endpoint), but unlike the previous study, did not demonstrate an overall survival advantage at 3 years ($P = .33$) [136]. A *post hoc* pooled analyses of these two trials ($n = 225$) maintained an overall survival advantage for the interventional group, with median survival being 18.9 months in the placebo arm and 23.2 months in the sipuleucel-T arm (hazard ratio 1.5; $P = .01$) [136]. However, because overall survival was not the primary endpoint in either trial, the FDA did not grant approval of this treatment.

Ongoing at the time of initial FDA review of sipuleucel-T, a multi-center phase III randomized, double-blind, placebo-controlled study (IMPACT) powered to assess overall survival as its primary endpoint was designed. The initial results of this trial, which accrued a total of 512 patients, were recently reported at a national meeting. According to the investigators, sipuleucel-T demonstrated a modest but real survival advantage compared to placebo in men with metastatic CRPC (median survival 25.8 months versus 21.7 months, hazard ratio 0.78; $P = .03$) [137]. Three-year survival was also improved by 38% with sipuleucel-T compared to placebo (31.7% versus 23.0%). Re-examination of the data from this trial by the FDA is expected before a decision about its approval is made.

3.2. GVAX

Prostate GVAX® is based on the demonstration in mouse melanoma models of improved tumor rejection when the irradiated tumor vaccine expressed the cytokine GM-CSF

compared with other cytokine adjuvants [138,139]. This form of immunotherapy uses inactivated allogeneic prostate cancer cell lines (PC3 and LNCaP) which have been modified through adenoviral transfer to secrete GM-CSF and irradiated to prevent further cell division [140]. The advantage with this whole cell-based approach is that the vaccine can be manufactured in large quantities and that multiple tumor antigens can be targeted simultaneously. However, because of the relative weakness of individual antigens, repeated intradermal dosing is necessary.

Two uncontrolled single-arm phase II studies in men with asymptomatic metastatic CRPC have shown anti-tumor effects of prostate GVAX, one demonstrating an overall survival of 26.2 months (n = 34) and the other showing an overall survival ranging from 20.0 to 29.1 months (n = 80) depending on dosing regimen [141,142]. In both studies, the proportion of patients who generated an antibody response to one or both cell lines increased with the dose of vaccine given, and no dose-limiting or autoimmune toxicities were seen. The most common adverse events in both studies were injection-site erythema, fatigue, malaise, myalgias, and arthralgias.

Based on these promising findings, two large randomized phase III studies of GVAX immunotherapy (VITAL-1 and VITAL-2) were designed. VITAL-1 involved 626 men with asymptomatic chemotherapy-naïve CRPC, and randomized them to GVAX or docetaxel/prednisone, with the primary endpoint being overall survival. VITAL-2 was planned initially to enroll 600 patients with symptomatic metastatic CRPC, randomizing them to docetaxel/prednisone or docetaxel/GVAX. Both trials were terminated early because of data observed at the time of interim analyses suggesting that the survival improvements initially hypothesized were unlikely to be observed if the trials were to be continued [143]. Moreover, in the VITAL-2 study, mortality appeared to be higher in patients on the experimental arm receiving docetaxel/GVAX [144].

3.3. PROSTVAC™

Poxviral vectors have also been employed to treat patients with CRPC by using a platform of recombinant PSA inserted into fowlpox and vaccinia viral vectors (designated rF-PSA and rV-PSA, respectively). PROSTVAC™ consists of these constructs of rF-PSA and rV-PSA and also contains a triad of costimulatory transgenes known as TRICOM™: intercellular adhesion molecule-1, B7–1, and leukocyte function-associated antigen-3 [145]. A phase I study using a priming dose of PROSTVAC followed by a booster dose 4 weeks later in 10 chemotherapy-naïve patients with CRPC produced minimal toxicities (injection site reactions, pruritus, fevers/chills, fatigue, nausea) and resulted in stable PSA levels for 8 weeks in 4 men (40%) [146]. A randomized, double-blind phase II trial of PROSTVAC (one priming dose, then six boosts over 24 weeks) versus empty vector in 122 men with metastatic CRPC failed to show a difference in the primary endpoint of progression-free survival between treatment arms (P = .56) [147]. However, updated 3-year results of this trial revealed an overall survival benefit in the PROSTVAC arm (median survival 24.5 months versus 16.0 months; P = .016) [148]. A randomized phase III cooperative group study using docetaxel with or without PROSTVAC as first-line therapy for men with metastatic CRPC is now being planned.

3.4. CTLA-4 inhibition

Another immune modulating approach that has recently emerged is the blockade of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) using monoclonal antibodies. CTLA-4 is a co-stimulatory molecule on the surface of T lymphocytes that functions as a negative regulator of T cell activation, leading to attenuation of T cell responses against tumor cells [149]. CTLA-4 blockade has previously been shown to potentiate T-cell effects and induce tumor rejection in mouse models [150]. A randomized phase II trial in first-line CRPC evaluated the anti-CTLA-4 antibody, ipilimumab, used alone or in combination with a single dose of docetaxel. This study showed an equal number of PSA responses (and no radiological responses) in each arm, suggesting that there was no apparent enhancement of this approach by adding docetaxel [151]. Two other studies using ipilimumab in men with metastatic CRPC are currently underway. The first is a phase I/II dose-escalating study of ipilimumab used as monotherapy [152]; the second is a phase I study testing the combination of ipilimumab and prostate GVAX [153]. A phase III study in docetaxel-refractory patients is also being planned. Common adverse events with ipilimumab include fatigue, rash, pruritus, nausea, constipation, and weight loss. Rare immune-based toxicities are adrenal insufficiency, hepatitis, and autoimmune colitis.

3.5. PD-1 blockade

Another co-inhibitory receptor molecule expressed on activated T lymphocytes and functioning as an immune checkpoint is programmed death-1 (PD-1). When PD-1 is bound by its ligand, T cell activation and proliferation are inhibited, resulting in suppression of anti-tumor immune responses [154]. Expression of the PD-1 ligand has been described on a variety of human tumor cells including prostate cancer, leading to decreased tumor-specific immunogenicity [155]. In addition, expression of the PD-1 ligand correlates with a poorer prognosis in many human malignancies. MDX-1106, a fully human anti-PD-1 blocking antibody, is the first agent in its class to reach human testing. Phase I trials using MDX-1106 in patients with refractory metastatic solid tumors (including metastatic CRPC) are currently being conducted [156]. Common side effects of this agent include subclinical hypothyroidism and autoimmune arthritis. Phase II studies of MDX-1106 have not yet been launched.

4. Conclusion

Although its benefits are modest, docetaxel chemotherapy remains the standard of care for the treatment of metastatic CRPC in 2009. As such, docetaxel has become the backbone of current drug development strategies in CRPC, either as the comparator arm in clinical trials or as the foundation on which novel targeted agents are added. To this end, the most promising agents in the pre-chemotherapy setting are likely to be docetaxel-bevacizumab, docetaxel-atrasentan, and sipuleucel-T. In addition, the management of docetaxel-refractory CRPC remains an area of unmet clinical need. Among the most promising agents in this setting are abiraterone and MDV-3100. Importantly, it should be noted that blocking one signaling pathway in a prostate cancer cell (e.g. the PI3K/mTOR pathway) often leads to reciprocal activation of a parallel or upstream pathway (e.g. the IGF-1R pathway) via negative feedback loops. One way to overcoming this phenomenon is to use combinations of

agents that target separate pathways or different parts of the same pathway. For example, combining mTOR blockade with upstream inhibition of IGF-1R or PI3K/Akt may abrogate feedback induction and enhance anti-tumor effects.

The medical community now eagerly awaits the results of the CALGB 90401 trial (a phase III study of docetaxel-bevacizumab versus docetaxel alone) and the FDA's decision on the IMPACT trial (a phase III study of the sipuleucel-T vaccine versus placebo). In addition, preliminary results from phase III trials of abiraterone are on the horizon. Meanwhile, continued advances in our understanding of prostate cancer progression, through both genomics and cancer stem cell biology, will certainly further expand our armamentarium of molecularly targeted therapeutics in the future. With such a plethora of new approaches for CRPC in clinical development, the current challenge is to prioritize and enroll patients in clinical trials with standardized endpoints [157], to quickly eliminate marginal agents, and to enable promising therapies to be taken swiftly to definitive phase III registrational studies. With a focus on small but incremental health benefits and an emphasis on meaningful clinical trial endpoints, metastatic CRPC can hopefully be transformed into a chronic symptom-free condition.

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Table 1

Selected ongoing clinical trials of targeted therapies in castration-resistant prostate cancer.

Target	Agent	Phase	Summary of trial	Identifier
PI3K/mTOR	Everolimus	II	Docetaxel + everolimus for first-line metastatic CRPC	NCT00459186
	Deforolimus	II	Single-agent deforolimus for second-line metastatic CRPC	NCT00110188
VEGF	Bevacizumab	III	Docetaxel ± bevacizumab for first-line metastatic CRPC	NCT00110214
VEGF receptor	Sorafenib	II	Docetaxel + sorafenib for first-line metastatic CRPC	NCT00589420
	Sunitinib	II	Docetaxel + sunitinib for first-line metastatic CRPC	NCT00137436
		III	Sunitinib versus placebo for second-line metastatic CRPC	NCT00676650
	Vatalinib	II	Single-agent vatalinib for non-metastatic CRPC	NCT00134355
VEGF-Trap	Aflibercept	III	Docetaxel ± aflibercept for first-line metastatic CRPC	NCT00519285
Tumor-VDA	DMXAA	II	Docetaxel ± DMXAA for first-line metastatic CRPC	NCT00111618
PDGFR	Imatinib	II	Docetaxel ± imatinib for first-line metastatic CRPC	NCT00080678
EGFR/Her2	Gefitinib	II	Gefitinib + everolimus for first-line metastatic CRPC	NCT00085566
	Lapatinib	II	Single-agent lapatinib for non-metastatic CRPC	NCT00246753
Bcl-2	Oblimersen	II	Docetaxel ± oblimersen for first-line metastatic CRPC	NCT00085228
	AT-101	II	Docetaxel ± AT-101 for first-line metastatic CRPC	NCT00571675
IGF-1R	IMC-A12	II	Mitoxantrone + IMC-A12 for second-line metastatic CRPC	NCT00683475
	CP-751,871	II	Docetaxel + CP-751,871 for first- and second-line metastatic CRPC	NCT00313781
Endothelin receptor	Atrasentan	III	Docetaxel ± atrasentan for first-line metastatic CRPC	NCT00134056
	Zibotentan	III	Docetaxel ± zibotentan for first-line metastatic CRPC	NCT00617669
RANK ligand	Denosumab	III	Denosumab versus zoledronate for palliation in metastatic CRPC	NCT00321620
Vitamin D	Calcitriol	III	Docetaxel ± calcitriol for first-line metastatic CRPC (closed early)	NCT00273338
CYP17	Abiraterone	III	Abiraterone versus placebo for first-line metastatic CRPC	NCT00887198
		III	Abiraterone versus placebo for second-line metastatic CRPC	NCT00638690
Androgen receptor	MDV-3100	I/II	Single-agent MDV-3100 for non-metastatic or metastatic CRPC	NCT00510718
HDAC	Vorinostat	II	Single-agent vorinostat for second-line metastatic CRPC	NCT00330161
	Panobinostat	II	Single-agent panobinostat for second-line metastatic CRPC	NCT00667862
DNMT	Azacitidine	II	Docetaxel + azacitidine for second-line metastatic CRPC	NCT00503984
Immune therapy	Sipuleucel-T	III	Provenge® versus placebo for first-line metastatic CRPC	NCT00065442
	GVAX®	III	GVAX versus docetaxel for first-line metastatic CRPC (closed early)	NCT00089856
		III	Docetaxel ± GVAX for first-line metastatic CRPC (closed early)	NCT00133224
CTLA-4	Ipilimumab	III	Ipilimumab versus placebo for second-line metastatic CRPC	NCT00861614
PD-1	MDX-1106	I	Single-agent MDX-1106 for refractory metastatic solid tumors including CRPC	NCT00441337

Abbreviations: CRPC, castration-resistant prostate cancer; PI3K, phosphatidylinositol 3-kinase; mTOR, mammalian target of rapamycin; EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; HDAC, histone deacetylase; DNMT, DNA methyltransferase; RANK, receptor activator of nuclear factor κB; VEGF, vascular endothelial growth factor; VDA, vascular disrupting agent; IGF-1R, insulin-like growth factor type-1 receptor; CYP17, cytochrome P17 (17,20 lyase and 17α-hydroxylase); CTLA-4, cytotoxic T lymphocyte-associated antigen-4; PD-1, programmed death-1.