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Future Directions in Castrate-Resistant Prostate Cancer Therapy

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Abstract

Although several new therapies have recently become available for the treatment of castrate-resistant prostate cancer (CRPC), the disease remains universally incurable and demands novel therapeutic approaches. To this end, great strides have been made in our understanding of the biologic and molecular mechanisms driving prostate cancer growth and progression in the past few years, resulting in widespread clinical investigation of numerous new targeted therapies. This review will highlight some of the key therapeutic agents that (in the opinion of the authors) may have the largest effect on the future management of CRPC, with a focus on both molecular targets and clinical trial design. These agents include angiogenesis inhibitors, mTOR pathway inhibitors, apoptosis-inducing drugs, IGF pathway inhibitors, Src family inhibitors, Hedgehog pathway antagonists, epigenetic therapies, PARP inhibitors, and prodrug approaches. The future of CRPC therapy appears brighter than ever before.

Keywords

Clinical trials; CRPC; Drug development; Targeted therapy

Introduction

Castrate-resistant prostate cancer (CRPC) is the lethal form of this disease, yet until recently, therapies that improved survival in this setting were limited. In the past several months, 2 new treatment options were added to the existing chemotherapy standard (ie, docetaxel) for patients with metastatic CRPC. One of these, the immunotherapy product sipuleucel-T, has been approved for use in men with minimally symptomatic metastatic CRPC and the other, the novel taxane cabazitaxel, is indicated for patients with disease progression following docetaxel administration. Encouragingly, a panoply of additional agents (eg, the hormonal drugs abiraterone and MDV-3100, the bone-targeted agent denosumab, and the immune checkpoint inhibitor ipilimumab) have made their way into pivotal phase III trials and may also add to the therapeutic arsenal in the near future. These therapies have created a dynamic shift in the previously static landscape of therapeutic possibilities for men with advanced prostate cancer. Still, CRPC remains incurable, and as a result, new druggable targets

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continue to be explored at an increasingly rapid pace. The pursuit of such novel targeted therapies likely represents the future of prostate cancer drug development.

The number of agents in various stages of clinical exploration for the treatment of CRPC is higher than ever before. This has been made possible by our accelerated understanding of the biologic and molecular mechanisms underpinning prostate cancer growth and spread, which has fueled an expansion of research on new therapeutic approaches. This review will highlight some novel targeted therapies that may be the wave of the future in the management of CRPC, focusing on mechanism of action and developmental status of some key clinical compounds that are currently in human clinical trials. Advances in chemotherapeutic approaches, hormonal manipulations, bone-targeting interventions, and immunotherapeutic strategies will not be discussed here, and will be highlighted by other authors in this issue.

Angiogenesis Inhibitors

Bevacizumab

Tumor angiogenesis is thought to be an important process in prostate cancer progression, and elevated plasma levels of vascular endothelial growth factor (VEGF) have been correlated with advanced clinical stage and decreased survival.^{1,2} Additionally, antibodies to VEGF slow prostate xenograft growth rates, especially when combined with chemotherapy.^{3,4} Encouraging results from several phase II studies combining the anti-VEGF antibody bevacizumab with docetaxel^{5,6} led to the conduct of a pivotal phase III trial (CALGB 90401) evaluating docetaxel plus either bevacizumab or placebo in 1050 men with metastatic CRPC. Disappointingly, although an improvement in progression-free survival (PFS) was seen in the docetaxel-bevacizumab arm of this study (9.9 months vs. 7.5 months; $P < .0001$), this did not translate into an overall survival (OS) advantage (22.6 months vs. 21.5 months; $P = .18$).⁷ However, these results do not indicate that bevacizumab may never have a role in the treatment of CRPC. Future development of this agent may focus on combining it with other classes of angiogenesis inhibitors or other chemotherapeutic drugs whose toxicities do not overlap with those of bevacizumab. Alternatively, evaluation of serological angiogenic markers from men treated on the CALGB 90401 trial may uncover a subset of patients that derive a survival advantage with the addition of bevacizumab.

Tyrosine Kinase Inhibitors

A second approach has focused on tyrosine kinase inhibitors (TKIs), agents that block angiogenic growth factor targets such as the VEGF receptor. In phase II studies involving men with metastatic CRPC, oral sorafenib was shown to prevent radiologic progression and even caused regression of bone metastases in some patients, but without inducing prostate-specific antigen (PSA) declines.^{8,9} Similarly, sunitinib produced some partial radiographic responses but had minimal effect on PSA levels in men with both chemotherapy-naïve and docetaxel-pretreated CRPC.^{10,11} A definitive phase III study using single-agent sunitinib versus placebo in patients with docetaxel-refractory disease is now being conducted (Table 1). Finally, a novel multikinase inhibitor, vatalanib, is currently being tested in a phase II

study in combination with docetaxel for patients with metastatic CRPC; radiologic responses rather than PSA declines have been chosen as the primary endpoint in this trial.

Aflibercept

An alternative antiangiogenic strategy is to use VEGF decoy receptors (VEGF-Trap) to saturate circulating VEGF, preventing it from binding to its natural receptor. The lead agent in this class is aflibercept, a recombinant decoy fusion protein of VEGF receptors-1 and -2 and the Fc fragment of IgG1.¹² In a phase I/II study of intravenous (I.V.) aflibercept combined with docetaxel in 54 heavily pretreated patients with advanced solid tumors,¹³ the partial response (PR) rate was 9%, while 59% of patients demonstrated stable disease (SD). Toxicities of this combination included neutropenia, hypertension, proteinuria, epistaxis, and dysphonia. A multicenter, placebo-controlled phase III trial of docetaxel with or without aflibercept for men with metastatic CRPC is currently under way (Table 1).

IMiDs

Thalidomide inhibits angiogenesis through multiple potential mechanisms, including inhibition of proangiogenic signals such as VEGF, basic fibroblast growth factor, interleukin-6, and tumor necrosis factor- α .¹⁴ In addition, this agent has T-cell costimulatory activity and immunomodulatory properties. Phase I/II studies using high doses of thalidomide have yielded low PSA response rates.¹⁵ However, in a randomized phase II trial of weekly docetaxel with or without low-dose thalidomide, PSA responses, time to disease progression, and OS appeared to be greater in the combination arm.¹⁶ Toxicities with thalidomide include deep venous thrombosis, sedation, neuropathy, constipation, and fatigue. Notably, a phase II trial using a 3-drug combination of docetaxel, thalidomide, and bevacizumab showed PSA responses in the 80% range, although neurotoxicity was prohibitive with this combination.¹⁷ Several phase I and II studies have also examined the related agent lenalidomide, which has been shown to produce PSA responses and partial radiographic responses, both when used alone and when combined with ketoconazole or docetaxel.^{18–21} This agent has less neurotoxicity than thalidomide but more myelosuppression. A placebo-controlled phase III trial of docetaxel with or without lenalidomide in patients with CRPC was recently launched (Table 1). Future studies using this class of agents in men with CRPC will probably focus on lenalidomide over thalidomide, because of the milder toxicity profile and lack of neurologic sequelae with lenalidomide, especially because these agents may be administered in combination or in sequence with docetaxel.

Tasquinimod

Another angiogenesis-inhibiting agent that has received renewed attention is the oral quinoline derivative tasquinimod. Although the antiangiogenic properties of this agent have been amply demonstrated in multiple in vitro and in vivo prostate cancer models,²² the exact mechanism of action of this drug remains elusive and appears to be unrelated to VEGF receptor inhibition. Impressively, a randomized double-blind placebo-controlled phase II study involving 200 patients with chemotherapy-naïve metastatic CRPC demonstrated that patients receiving tasquinimod had a median PFS of 7.6 months versus 3.2 months in those

receiving placebo ($P = .001$).²³ Adverse events with this agent included gastrointestinal disorders, fatigue, musculoskeletal pain, and asymptomatic elevations of pancreatic enzymes and inflammatory markers. Rare but serious toxicities were heart failure, myocardial infarction, stroke, and deep vein thrombosis. A phase III trial of tasquinimod in patients with CRPC is currently in development.

Tumor Vascular-Disrupting Agents

A final antiangiogenic strategy involves the use of agents that primarily act against established tumor blood vessels, disrupting vascular endothelial cells, and causing a range of subsequent antivascular effects.²⁴ The prototype in this class is 5,6-dimethylxanthoine-4-acetic acid (vadimezan), which was shown to act synergistically with docetaxel in human prostate cancer xenografts.²⁵ In a multicenter randomized phase II trial of docetaxel plus or minus I.V. vadimezan in 74 men with metastatic CRPC, > 30% PSA reductions were observed in 37% and 59% of patients in the control and interventional arms, respectively, and radiographic response rates were 9% and 23%, respectively.²⁶ Adverse events with vadimezan included neutropenia and cardiac toxicities (supraventricular tachycardia, myocardial ischemia).

PI3K/Akt/mTOR Pathway Inhibitors

mTOR Inhibitors

Although mammalian target of rapamycin (mTOR) inhibitors probably have minimal single-agent activity in advanced CRPC,²⁷ the combination of these drugs with docetaxel is attractive given their ability to reverse chemotherapy resistance in prostate cancer cell lines.²⁸ In addition, these agents induce apoptosis when administered in combination with chemotherapy in patients who have activation of the Akt pathway as a result of PTEN mutation/loss or other genetic alterations.²⁹ Several mTOR inhibitors have entered human clinical testing. One of these, everolimus, is currently being evaluated in combination with docetaxel for the treatment of metastatic CRPC in phase I/II trials (Table 1).^{30,31} In addition, temsirolimus is being tested in combination with antiandrogen therapy in men with chemotherapy-naïve CRPC,³² and also as maintenance therapy after response to docetaxel treatment.³³ A third mTOR inhibitor, ridaforolimus, is also being investigated in the phase II setting as monotherapy in men with taxane-refractory disease. Toxicities of mTOR inhibitors include maculopapular rash, hypertriglyceridemia, hyperglycemia, allergic reactions, pedal edema, mucositis, and thrombocytopenia.

Akt Inhibitors

Advanced prostate cancers frequently demonstrate elevated levels of phosphorylated (activated) Akt.³⁴ In addition to promoting cell survival through the inhibition of apoptosis, the Akt pathway regulates cell growth, proliferation, and angiogenesis via mTOR, and facilitates translation of signals such as c-Myc, cyclin D, and VEGF.³⁵ Disappointingly, a phase II study of an early Akt inhibitor, perifosine, failed to show any clinical activity when used as monotherapy in 19 men with metastatic CRPC.³⁶ A novel oral allosteric Akt inhibitor, MK2206, has recently completed phase I testing,³⁷ and a phase II cooperative group study of this agent in patients with noncastrate PSA-recurrent prostate cancer after

local therapy will soon be launched. A further phase I study of MK2206 combined with docetaxel in patients with advanced solid tumors is ongoing (Table 1). Although we are still in the early days of development of this class of agents, optimal use of these drugs will likely require careful selection of patients based on molecular tumor characteristics, and may rely on rational combinations of different drugs targeting separate components of the PI3K/Akt/mTOR pathway.

Drugs Targeting Apoptosis

AT-101

The antiapoptotic factor Bcl-2 is an attractive target in the treatment of CRPC, as overexpression of Bcl-2 induces the transition to androgen-independent cell growth,³⁸ and confers resistance to many antineoplastic agents including taxanes.³⁹ AT-101 (R-gossypol acetate) is an oral agent derived from the cottonseed plant that inhibits the function of all Bcl-2–related proteins (Bcl-2, Bcl-xL, Mcl-1, and Bcl-w), lowering the threshold for cancer cells to undergo apoptosis.⁴⁰ Preclinically, AT-101 has shown antitumor activity in a variety of tumor types including prostate cancer.⁴¹ In a phase I/II study of AT-101 monotherapy in 23 men with metastatic CRPC, 50% PSA declines were observed in only 9% of men while no patient had a radiologic response.⁴² Toxicities related to AT-101 were diarrhea, fatigue, nausea, anorexia, leukopenia, and hypophosphatemia. More favorable results were seen in a second phase I/II study combining AT-101 together with docetaxel in patients with chemotherapy-naïve CRPC; in that study 89% of men showed a 50% PSA decline and 33% demonstrated partial radiologic responses.⁴³ A multicenter randomized phase II study evaluating docetaxel plus or minus AT-101 in the first-line treatment of metastatic CRPC has completed accrual of 220 patients, and OS results are expected to be reported shortly (Table 2).

Custirsen

Clusterin is a stress-induced antiapoptotic chaperone protein expressed in various cancers including prostate cancer,⁴⁴ and functioning as a cytoprotective factor similar to ATP-independent heat shock proteins.⁴⁵ It mediates its antiapoptotic effects through mechanisms that include inhibition of the proapoptotic protein Bax, prevention of protein aggregation, and enhanced nuclear factor- κ B activity.^{46,47} In cancer, expression of clusterin increases after treatment with androgen ablation or chemotherapy,^{48,49} conferring a more resistant phenotype. In addition, clusterin expression correlates with higher Gleason scores and progression to CRPC.⁴⁹ Custirsen is an antisense oligonucleotide drug that inhibits clusterin at the mRNA level by binding to its translation initiation site, increasing sensitivity to androgen deprivation and chemotherapy in prostate cancer cell lines and xenograft models.^{50,51} A phase I study of I.V. custirsen given together with docetaxel established the optimal dosing and safety of this combination, and also resulted in decreased serum clusterin levels in treated patients.⁵² In a randomized phase II study of docetaxel with or without custirsen in 82 men with metastatic CRPC, PSA responses (58% vs. 54%) as well as objective responses (19% vs. 25%) and PFS (7.3 months vs. 6.1 months) were similar in both arms. However, OS trended in favor of the custirsen arm (23.8 months vs. 16.9 months; $P = .06$; HR 0.61, 95% CI, 0.36–1.02), although survival was not the primary endpoint of

this study.⁵³ In addition, custirsen decreased median serum clusterin levels by 26%. Adverse events associated with custirsen included fatigue, leukopenia, elevated serum creatinine, fever, rigors, diarrhea, and rash.⁵³ Another phase II study of second-line chemotherapy plus custirsen in men with docetaxel-pretreated CRPC has recently completed accrual (Table 2). A registrational phase III trial of docetaxel retreatment with or without custirsen in the second-line management of patients with docetaxel-refractory disease has recently opened. Indeed, custirsen appears to be one of the most promising apoptosis-targeting agents currently in clinical development for the treatment of prostate cancer.

Survivin Inhibitors

A final class of drugs mediating their effect via the apoptotic pathway are the survivin antagonists. Survivin, one of the most cancer-specific proteins identified to date, has been shown to inhibit apoptosis as well as to enhance cell proliferation and promote tumor angiogenesis in multiple tumor types including prostate cancer.⁵⁴ Because of its marked upregulation in malignant tissues but not in normal cells, and the observation that its suppression leads to inhibition of tumor growth, survivin has attracted attention as a promising target for anticancer therapies. Two agents in this class that are currently in clinical development include LY2181308 (an antisense oligonucleotide that binds to survivin mRNA)⁵⁵ and YM155 (a small molecule survivin inhibitor).⁵⁶ Several phase II studies investigating these 2 drugs in men with metastatic CRPC are under way or have recently completed accrual (Table 2).

IGF Pathway Inhibitors

Cixutumumab

Insulin-like growth factor receptor-1 (IGF-1R) and its ligands may play a key role in prostate carcinogenesis through mechanisms that involve mitogenesis, anti-apoptosis, and cellular transformation. IGF-1R is often overexpressed in prostate tumors and can mediate cell proliferation and resistance to androgen ablation.^{57,58} Therapeutic monoclonal antibodies that bind to the extracellular domain of IGF-1R can potentially inhibit the function of this receptor.⁵⁹ In prostate cancer cell lines as well as in xenograft models, such antibodies have been shown to inhibit growth of both androgen-dependent and -independent tumors.^{60,61} Cixutumumab is a fully human IgG1 monoclonal antibody that specifically targets IGF-1R, inhibiting ligand binding and IGF signaling.⁶² In a phase II study of I.V. cixutumumab in 31 men with asymptomatic metastatic CRPC, 29% of patients demonstrated lack of radiographic progression after 6 months, and a greater number had PSA responses.⁶³ Toxicities of this agent were fatigue, hyperglycemia, thrombocytopenia, hyperkalemia, and muscle spasms. A phase II study combining cixutumumab with mitoxantrone in the second-line treatment of docetaxel-refractory disease is currently underway (Table 3). A combination trial of cixutumumab plus temsirolimus in the prechemotherapy space has also recently opened.

Figitumumab

Figitumumab is the second fully human anti-IGF-1R IgG2 monoclonal antibody to enter clinical testing.⁶⁴ A phase Ib study of I.V. figitumumab given in combination with docetaxel

to men with metastatic CRPC has been completed. In that study, 4 of 18 patients (22%) had a radiographic PR, and 12 men (67%) had disease stabilization for 6 months.⁶⁵ In addition, 9 of 10 patients with measurable circulating tumor cell (CTC) counts at baseline had a 30% decline in CTC numbers. Toxicities of this combination regimen were leukopenia (including neutropenia), fatigue, diarrhea, and hyperglycemia. A phase II study of figitumumab combined with docetaxel in men with chemotherapy-naïve (arm A) and docetaxel-resistant (arm B) CRPC is in progress (Table 3).

Src Kinase Inhibitors

Dasatinib

Src is a non-receptor tyrosine kinase signal transduction protein that is involved in multiple pathways in prostate cancer, and is important in tumor cell proliferation, migration, angiogenesis, survival, and transition to androgen-independent growth.⁶⁶ Src also controls normal and abnormal osteoclast activity, and may be implicated in development and progression of bone metastases.⁶⁷ Dasatinib is an oral inhibitor of multiple oncogenic kinases including Src. In experimental studies, dasatinib suppressed proliferation of prostate cancer cell lines,⁶⁸ and inhibited adhesion, migration, and invasion.⁶⁹ In addition, dasatinib reduced tumor growth and lymph node involvement in a prostate cancer mouse xenograft model.⁷⁰ A phase II study of dasatinib monotherapy in men with metastatic CRPC did not show significant PSA responses, but 19% of patients were free of disease progression at 6 months. Additionally, more than half of subjects had 40% decreases in urinary N-telopeptide levels (a marker of bone resorption), and 60% showed reductions in bone alkaline phosphatase.⁷¹ In a separate phase I/II study combining dasatinib with docetaxel in a similar patient population, PSA responses were observed in 41% of participants, and 32% of patients with bone metastases showed improvements in bone scans.⁷² A placebo-controlled randomized phase III OS study evaluating this combination in men with metastatic chemotherapy-naïve CRPC is now accruing patients (Table 4).

Saracatinib

Another oral Src kinase inhibitor, saracatinib, has also been shown to inhibit Src phosphorylation and tumor growth in a murine xenograft model of prostate cancer.⁷³ In a phase II study of single-agent saracatinib in advanced CRPC, 18% of patients had transient PSA reductions but all were < 30%.⁷⁴ Adverse events with this agent included transaminase elevations, emesis, and lymphopenia. A randomized phase II study of saracatinib versus zoledronate in patients with bone-metastatic CRPC is in progress (Table 4).

KX2-391

A recent addition to the Src inhibitor class is the oral drug, KX2-391, which uniquely targets the peptide-binding domain and does not compete with ATP for binding.⁷⁵ This agent has been shown to suppress oncogenic proliferation in multiple cancers in vitro and in vivo, including prostate cancer.⁷⁶ In a phase I trial of KX2-391 monotherapy for patients with advanced refractory malignancies, 1 of 3 men with CRPC had an 81% decline in his PSA level.⁷⁷ Toxicities with this drug included fatigue, transaminase elevation, hypokalemia,

vomiting, and myelosuppression. A phase II study of single-agent KX2-391 in men with bone-metastatic chemotherapy-naïve CRPC is currently enrolling patients (Table 4).

Hedgehog Inhibitors

Vismodegib

The Hedgehog (Hh) signaling pathway is a developmental pathway that regulates epithelial-mesenchymal interactions, cell proliferation, survival, and angiogenesis.⁷⁸ Constitutive overexpression of the Hh ligand has been demonstrated in a number of malignancies including prostate cancer.^{79,80} In preclinical models, Hh pathway activation renders prostate epithelial cells tumorigenic, and aberrant Hh activity is seen in most advanced and metastatic prostate tumors, including CRPC.^{81,82} In vitro and in vivo experiments have shown that Hh pathway inhibition decreases prostate cancer cell proliferation and invasiveness while inducing apoptosis.⁸³ Similar results were seen in a prostate cancer xenograft model exposed to inhibitors of Hh-mediated transcription.⁸⁴ Vismodegib is the first drug in this class to reach clinical testing,⁸⁵ and a phase I trial of single-agent vismodegib in patients with advanced solid tumors demonstrated impressive clinical activity against metastatic medulloblastoma and basal cell carcinoma,^{86,87} tumors known to harbor activating mutations of Hh pathway genes. A presurgical phase II study randomizing men with localized prostate cancer to androgen ablation with or without vismodegib before prostatectomy was recently launched (Table 5).

Itraconazole

Another agent with surprising Hh-inhibitory activity is the antifungal drug itraconazole. In vitro studies have shown that itraconazole potently inhibits proliferation of the Hh reporter cell line NIH 3T3, while other azole antifungals (eg, ketoconazole) do not possess this activity. In addition, itraconazole induced tumor growth inhibition in a mouse medulloblastoma model (ptch1^{+/-} p53^{-/-}) that has constitutive overactivation of Hh signaling.⁸⁸ In this murine allograft model, serum levels of itraconazole required for tumor inhibition were equivalent to those achieved in man using 600 mg of itraconazole daily. In addition, it has been shown that itraconazole possesses antiangiogenic and mTOR-inhibitory properties.^{89,90} A randomized phase II trial examining 2 doses of itraconazole (200 mg vs. 600 mg) in men with metastatic CRPC has just completed accrual (Table 5).

Epigenetic Approaches

HDAC Inhibitors

Histone deacetylases (HDACs) are regulators of histone acetylation status which is critical for androgen receptor-mediated transcriptional activation of genes governing cell survival, proliferation, differentiation, and apoptosis.⁹¹ Vorinostat is an oral HDAC inhibitor that has shown antitumor activity in prostate cancer cell lines and animal models.⁹² However, a phase II study of vorinostat monotherapy in men with docetaxel-refractory CRPC did not show significant PSA or radiologic responses and was associated with a high frequency of adverse events including fatigue, emesis, anorexia, diarrhea, and weight loss.⁹³ A second HDAC inhibitor, panobinostat, has completed phase I testing (used both as an oral and

intravenous agent) in combination with docetaxel^{94,95}; the I.V. formulation has been chosen for future development. A phase II trial of single-agent I.V. panobinostat in docetaxel-refractory disease is ongoing (Table 5).

DNMT Inhibitors

DNA methylation of key tumor suppressor genes represents another epigenetic mechanism by which prostate cancer may progress to a castration-resistant state.⁹⁶ The hypomethylating agent azacitidine is a subcutaneously administered drug that exerts its antineoplastic effects by inhibiting DNA methyltransferases (DNMTs) in promoter regions of genes, leading to reversal of gene silencing.⁹⁷ In experimental in vitro and in vivo prostate cancer models, azacitidine reverses resistance to androgen ablation and chemotherapy,⁹⁸ making this agent attractive for clinical trial development. To this end, a phase II study of azacitidine in men with chemotherapy-naïve CRPC caused lengthening of PSA doubling times in 65% of patients and resulted in a median PFS of 12.6 weeks.⁹⁹ Toxicities of this agent included fatigue and neutropenia. Another phase II study evaluating the combination of docetaxel and azacitidine in men with docetaxel-pretreated CRPC is now underway (Table 5).

PARP Inhibitors

Olaparib

PARPs are a family of enzymes that mend single-strand DNA breaks through the repair of base excisions. PARP inhibition leads to accumulation of single-strand DNA breaks which, if left unchecked, lead to double-strand DNA breaks at replication forks.¹⁰⁰ These double-strand breaks are repaired through the process of homologous recombination, mediated in part by the tumor suppressor proteins BRCA1 and BRCA2. Preclinical studies have shown that *BRCA1/2* mutation combined with PARP inhibition creates a “synthetic lethality” for such cells.¹⁰¹ This results in exquisite sensitivity of *BRCA1/2* mutant cells to PARP inhibitors. Another group of tumors that show increased sensitivity to PARP inhibition are those that harbor PTEN loss, a frequent occurrence in CRPC. PTEN null tumors exhibit genomic instability because of downregulation of Rad51 and impaired homologous recombination, or defects in cell cycle checkpoints.¹⁰² Olaparib was the first PARP inhibitor to enter clinical trials. In a phase I study of oral olaparib used in 22 patients with *BRCA1/2*-mutated tumors, this agent produced notable responses in several subjects including a > 50% PSA decline and resolution of bone metastases in a patient with *BRCA2*-related CRPC.¹⁰³ Toxicities with this agent include fatigue/somnolence, mood alterations, thrombocytopenia, and gastrointestinal symptoms. A larger phase II study of olaparib in patients with advanced *BRCA1/2*-mutated cancers is ongoing (Table 5).

ABT-888

Another important property of PARP inhibitors is their ability to enhance the activity of DNA-damaging cytotoxic agents (eg, alkylators, platinum, topoisomerase inhibitors).¹⁰⁴ To this end, the addition of the PARP inhibitor ABT-888 to temozolomide potentiates the antineoplastic effects of the alkylating agent in several cancer cell lines as well as animal xenograft models.¹⁰⁵ This has led to the design of a single-arm phase II study examining the

combination of oral ABT-888 and oral temozolomide in men with metastatic CRPC who have progressed after 1–2 previous chemotherapies (Table 5). Adverse events with ABT-888 are minimal, and no dose-limiting toxicities have been reported in phase I trials.

Pro-Drug Approaches

G-202

An intriguing notion in cancer treatment is the use of prodrug chemotherapy, aiming to achieve higher concentrations of cytotoxic or biologically active agents in tumors while sparing normal tissues. This can be accomplished when an inert form of a cytotoxin, the prodrug, is converted to an active agent at the tumor site. G-202 is a prodrug of thapsigargin, a non-cell-type specific toxin derived from the plant *Thapsia garganica* that has the ability to kill a broad spectrum of cancer cell lines and normal endothelial cells.¹⁰⁶ It consists of a cytotoxic analogue of thapsigargin linked to a masking peptide that inhibits its biologic activity until proteolytic cleavage occurs at the tumor site.¹⁰⁷ The masking peptide of G-202 is a substrate for prostate-specific membrane antigen (PSMA) which is found only on prostate cancer cells and solid tumor endothelial cells. When inactive G-202 reaches a PSMA-expressing cell, proteolytic cleavage by PSMA results in release of the thapsigargin analogue into the cancer cell where it induces a pronounced increase in the concentration of cytosolic calcium through blockade of the sarcoplasmic-endoplasmic reticulum calcium ATPase (SERCA) pump.¹⁰⁸ This increase in intracellular calcium leads to induction of apoptosis and cell death. In preclinical studies, G-202 administration in mice bearing human tumor xenografts (including PSMA-producing prostate cancer xenografts) has been shown to result in rapid tumor regression or growth inhibition.¹⁰⁹ A first-in-man phase I trial of I.V. G-202 in patients with advanced solid tumors has recently been launched (Table 5).

Conclusion

With an ever growing number of agents now available for the management of CRPC, and an explosion of novel targeted therapies making their way through the developmental pipeline, several new challenges arise. First, it must be determined how these approved and experimental therapies should best be sequenced in individual patients with CRPC. Second, strategies will need to be developed to optimally combine agents in a rational and scientific manner, taking advantage of knowledge of negative feedback loops to overcome resistance to monotherapies. Third, smarter trials must be designed with the goal of quickly and reliably identifying agents that do not hold promise, while enabling those that do to move swiftly to registrational studies. Finally, more careful patient selection based on clinical or molecular characteristics should be performed to identify the subset of men most likely to respond to a particular targeted therapy. 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 for CRPC in the future.

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Table 1
Selected Ongoing Clinical Trials of Drugs Targeting the Angiogenic and mTOR Pathways in Castration-Resistant Prostate Cancer

Target	Drug	Toxicities	Dose	Phase	Summary of Trial	Lead Site	Identifier
Angiogenesis Inhibitors							
VEGF receptor	Sorafenib	Fatigue, diarrhea, rash, hypertension, hand-foot syndrome	400 mg orally twice a day	II	Docetaxel + sorafenib for first-line metastatic CRPC	University of Pennsylvania	NCT00589420
	Sunitinib	Fatigue, diarrhea, rash, hypertension, nausea, leukopenia	37.5 mg orally daily (2 of 3 weeks)	II	Docetaxel + sunitinib for first-line metastatic CRPC	MD Anderson Cancer Center	NCT00137436
		Fatigue, diarrhea, rash, hypertension, nausea, leukopenia	37.5 mg orally daily	III	Sunitinib versus placebo for second-line metastatic CRPC	Global study	NCT00676650
	Vatalanib	Nausea, hypertension, proteinuria, leukopenia, transaminitis	1250 mg orally daily	II	Docetaxel + vatalanib for first-line metastatic CRPC	University of California San Francisco	NCT00293371
VEGF-Trap	Aflibercept	Fatigue, hypertension, proteinuria, headache, dysphonia, epistaxis	6 mg/kg I.V. every 3 weeks	III	Docetaxel ± aflibercept for first-line metastatic CRPC	Global study	NCT00519285
IMiDs	Lenalidomide	Fatigue, dizziness, rash, pruritus, diarrhea, cytopenias	25 mg orally daily (2 of 3 weeks)	III	Docetaxel ± lenalidomide for first-line metastatic CRPC	Global study	NCT00988208
PI3K/Akt/mTOR Pathway Inhibitors							
mTOR	Everolimus	Rash, edema, glycemia, lipidemia, cytopenias, asthenia	10 mg orally daily	II	Docetaxel + everolimus for first-line metastatic CRPC	Dana-Farber Cancer Institute	NCT00459186
	Temsirolimus	Rash, edema, asthenia, cytopenia, transaminitis, glycemia, lipidemia	25 mg I.V. every week	II	Temsirolimus + antiandrogen for second-line metastatic CRPC	Duke University	NCT00887640
	Ridaforolimus	Rash, fatigue, nausea, mucositis, transaminitis, glycemia, lipidemia	50 mg I.V. every week	II	Single-agent ridaforolimus for second-line metastatic CRPC	Dana-Farber Cancer Institute	NCT00110188
Akt	MK2206	Rash, nausea, fatigue, hyperglycemia	Dose escalation	I	Docetaxel + MK2206 for advanced refractory solid tumors	Royal Marsden Hospital	NCT00848718

Abbreviations: CRPC = castration-resistant prostate cancer; IMiDs = immunomodulatory drugs; I.V. = intravenous; mTOR = mammalian target of rapamycin; VEGF = vascular endothelial growth factor

Table 2
Selected Ongoing Clinical Trials of Drugs Targeting Apoptosis in Castration-Resistant Prostate Cancer

Target	Drug	Toxicities	Dose	Phase	Summary of Trial	Lead Site	Identifier
Apoptosis-Inducing Drugs							
Bcl-2	AT-101	Fatigue, diarrhea, emesis, leukopenia, hypophosphatemia	40 mg orally twice a day (days 1–3 every 21 days)	II	Docetaxel ± AT-101 for first-line metastatic CRPC	International study	NCT00571675
Clusterin	Custirsen	Rash, fever, rigors, diarrhea, leukopenia, elevated creatinine	640 mg I.V. every week	II	Second-line chemotherapy + custirsen for docetaxel-pretreated CRPC	University of Montreal	NCT00327340
		Rash, fever, rigors, diarrhea, leukopenia, elevated creatinine	640 mg I.V. every week	III	Docetaxel retreatment ± custirsen for docetaxel-refractory CRPC	Oregon Health and Science University	NCT01083615
Survivin	LY2181308	Fever, rigors, influenza-like illness, PTT prolongation	750 mg I.V. every week	II	Docetaxel ± LY2181308 for first-line metastatic CRPC	International study	NCT00642018
	YM155	Fatigue, diarrhea, fever, proteinuria, cytopenias	5 mg/m ² I.V. daily over 7 days	II	Docetaxel + YM155 for first-line metastatic CRPC	South Texas Oncology and Hematology	NCT00514267
		Fatigue, diarrhea, fever, proteinuria, cytopenias	5 mg/m ² I.V. daily over 7 days	II	Single-agent YM155 for second-line metastatic CRPC	Royal Marsden Hospital	NCT00257478

Abbreviations: CRPC = castration-resistant prostate cancer; I.V. = intravenous; PTT = partial thromboplastin time

Table 3
Selected Ongoing Clinical Trials of Drugs Targeting the IGF Pathway in Castration-Resistant Prostate Cancer

Target	Drug	Toxicities	Dose	Phase	Summary of Trial	Lead Site	Identifier
IGF-1R	IGF Pathway Inhibitors						
	Cixutumumab	Fatigue, hypoglycemia, thrombocytopenia, hyperkalemia	6 mg/kg I.V. every 1 week	II	Mitoxantrone + cixutumumab for second-line metastatic CRPC	University of Washington, Seattle	NCT00683475
		Fatigue, hypoglycemia, thrombocytopenia, hyperkalemia	6 mg/kg I.V. every 1 week	I/II	Cixutumumab + temsirolimus for first-line metastatic CRPC	Memorial Sloan-Kettering Cancer Center	NCT01026623
	Figitumumab	Fatigue, diarrhea, hypoglycemia, leukopenia	20 mg/kg I.V. every 3 weeks	II	Docetaxel + figitumumab for first- and second-line CRPC	International study	NCT00313781

Abbreviations: CRPC = castration-resistant prostate cancer; IGF-1R = insulin-like growth factor receptor-1; I.V. = intravenous

Table 4
Selected Ongoing Clinical Trials of Drugs Targeting Src Family Kinases in Castration-Resistant Prostate Cancer

Target	Drug	Toxicities	Dose	Phase	Summary of Trial	Lead Site	Identifier
Src Kinase Inhibitors							
Src	Dasatinib	Edema, rash, nausea, diarrhea, headache, cytopenias	100 mg orally daily	III	Docetaxel ± dasatinib for first-line metastatic CRPC	Global study	NCT00744497
	Saracatinib	Fatigue, diarrhea, emesis, transaminitis, renal failure, cytopenia	175 mg orally daily	II	Saracatinib versus zoledronate for bone-metastatic CRPC	Wake Forest University	NCT00558272
	KX2-391	Fatigue, transaminitis, emesis, hypokalemia, cytopenias	40 mg orally twice a day	II	Single-agent KX2-391 for bone-metastatic CRPC	Johns Hopkins University	NCT01074138

Abbreviation: CRPC = castration-resistant prostate cancer

Table 5
Selected Ongoing Clinical Trials of Other Miscellaneous Targeted Therapies in Castration-Resistant Prostate Cancer

Target	Drug	Toxicities	Dose	Phase	Summary of Trial	Lead Site	Identifier
Hedgehog Pathway Inhibitors							
Hedgehog	Vismodegib	Fatigue, hyponatremia, anorexia, weight loss, muscle spasms	270 mg orally daily	II	LHRH agonist ± vismodegib presurgery for prostate cancer	MD Anderson Cancer Center	NCT01163084
	Itraconazole	Fatigue, nausea, rash, diarrhea, anorexia, edema, hypokalemia	200 mg/600 mg orally daily	II	Itraconazole (200 vs. 600 mg) in first-line metastatic CRPC	Johns Hopkins University	NCT00887458
Epigenetic Therapies							
HDAC	Panobinostat	Fatigue, pruritus, emesis, dysgeusia, anorexia, diarrhea, cytopenias	15 mg/m ² I.V. (days 1 and 8 every 21 days)	II	Single-agent panobinostat for second-line metastatic CRPC	Memorial Sloan-Kettering Cancer Center	NCT00667862
DNMT	Azacitidine	Fatigue, fever, emesis, diarrhea, cytopenias, injection-site reactions	150 mg/m ² I.V. (days 1–5 every 21 days)	II	Docetaxel + azacitidine for second-line metastatic CRPC	University of Miami	NCT00503984
PARP Inhibitors							
PARP	Olaparib	Fatigue, emesis, dyspepsia, cytopenia, dysgeusia, anorexia	400 mg orally twice a day	II	Olaparib in BRCA-mutated solid tumors including CRPC	Chaim Sheba Medical Center, Israel	NCT01078662
	ABT-888	Fatigue, nausea, dysgeusia, dizziness, cytopenias	40 mg orally twice a day (days 1–7 every 28 days)	II	ABT-888 + temozolomide in docetaxel-refractory CRPC	University of Michigan	NCT01085422
Pro-Drug Approaches							
Thapsigargin	G-202	Unknown	Dose escalation	I	Single-agent G-202 in advanced solid tumors including CRPC	Johns Hopkins University	NCT01056029

Abbreviations: CRPC = castration-resistant prostate cancer; DNMT = DNA methyltransferase; HDAC = histone deacetylase; I.V. = intravenous; LHRH = luteinizing hormone-releasing hormone; PARP = poly (ADP-ribose) polymerase