Castration-Resistant Prostate Cancer: Targeted Therapies and Individualized Treatment

RAHUL AGGARWAL,a CHARLES J. RYANb

aDivision of Hematology/Oncology, Department of Medicine, and bHelen Diller Family Comprehensive Cancer Center, University of California, San Francisco, California, USA

Key Words. Prostatic neoplasms • Androgen receptor • Signal transduction • Investigational treatments

Disclosures: Rahul Aggarwal: None; Charles J. Ryan: Honoraria: sanofi-aventis, Novartis; Research funding/contracted research: Cougar Biotechnology, Novartis, ImClone.

The article describes a series of drugs that are in development for prostate cancer and, as such, are, by definition, investigational. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers.

ABSTRACT

Various molecular mechanisms have been implicated in the progression from hormone-sensitive to castration-resistant prostate cancer (CRPC). Novel targeted agents to treat CRPC have been developed that inhibit either androgen receptor (AR)-mediated signaling (AR antagonists and inhibitors of androgen synthesis) or non–AR-mediated signaling (inhibitors of Src, mammalian target of rapamycin, chaperone proteins, insulin-like growth factor-1 receptor, vascular endothelial growth factor, and endothelin-A receptor) pathways. However, variable efficacy has been observed in clinical trials, most likely because of the biologic heterogeneity of CRPC. To account for potential differences in disease biology, a more individualized approach to treatment, based on genomic and/or proteomic analyses of individual tumors, is being investigated. By identifying tumors with a characteristic molecular subtype and assigning treatment accordingly, it is hoped that a higher proportion of patients will benefit from targeted therapy. Additionally, lessons learned through the application of these technologies to prostate cancer may subsequently influence therapeutic development in other solid tumors. The Oncologist 2011;16:264–275

INTRODUCTION

Although most men who develop prostate cancer do not die from their disease, those who develop castration-resistant prostate cancer (CRPC) have a poor prognosis and are more likely to die from complications of metastatic disease than from comorbid illness. Approved systemic chemotherapies for CRPC provide limited benefits. Docetaxel, a taxane inhibitor of microtubule function, remains the standard first-line treatment based on two phase III trials that showed a median survival time of 18–19 months [1, 2]. Efforts are ongoing to develop various therapies targeting mechanisms behind tumor progression.
Several molecular pathways have been implicated in prostate cancer progression from localized disease that remains sensitive to androgen deprivation to CRPC, the lethal tumor phenotype. Pathways can be divided into those mediated by the androgen receptor (AR) and those without direct agonism of the AR [3]. Novel therapies have been rationally designed to target molecular pathways involved in oncogenesis and disease progression although results from trials have been mixed. The biologic heterogeneity of CRPC, including potential involvement of AR-mediated or AR-independent pathways, is a probable cause of the variable responses seen with targeted therapies. Arguably, a more rational approach could involve determining the biologic status of an individual tumor before therapy by assessing gene expression, hormone metabolism, or signaling activity, and directing treatment accordingly. This more individualized approach is being tested in early-phase clinical trials.

Here, we highlight several novel therapies for CRPC targeted to AR-mediated or non–AR-mediated pathways that have recently entered clinical trials, including the molecular rationale and available clinical data. We also summarize emerging evidence on the potential of individualized therapy for CRPC.

**TARGETING AR-MEDIATED SIGNALING**

Numerous lines of evidence indicate that persistent AR activation is an important mediator of disease progression in CRPC [3, 4]. Proposed mechanisms include: AR gene amplification or overexpression; AR gene mutation leading to promiscuous ligand/cofactor interaction; enhanced AR signal transduction mediated via coactivators; and endocrine or autocrine activation of the AR, for example, by adrenal androgens or intratumoral production of dihydrotestosterone (DHT). Established AR-directed approaches include AR antagonists, for example, bicalutamide and flutamide, in addition to agents that block the production of AR-activating hormones, for example, ketoconazole (Fig. 1). However, in patients with AR overexpression, traditional AR antagonists have shown agonistic activity toward the AR [5], which may explain prostate-specific antigen (PSA) decreases that sometimes occur following antiandrogen withdrawal [6, 7] and the limited additive effects of
antiandrogens combined with luteinizing hormone-releasing hormone–based therapies [8].

MDV3100 is a novel orally available AR antagonist with no known agonistic activity that was discovered through compound screening in a cellular model of prostate cancer activated by AR overexpression [9]. In a phase I/II trial, 140 patients with progressive CRPC were treated with doses in the range of 30–600 mg/day. In the chemotherapy-naïve and postchemotherapy subgroups, respectively, a 50% PSA decline from baseline occurred in 62% and 51%, a partial response (PR) in soft-tissue tumors evaluable by the Response Evaluation Criteria in Solid Tumors (RECIST) was achieved in 36% and 12%, stabilized bone disease at 12 weeks on bone scan occurred in 63% and 51%, and the median time to radiologic progression was not reached and 29 weeks (47 weeks in all patients) [10]. A randomized, placebo-controlled phase III study of MDV3100 monotherapy versus placebo in patients with docetaxel-prettreated CRPC has completed accrual; a second phase III study of MDV3100 monotherapy versus placebo in chemotherapy-naïve patients with CRPC has recently opened (Table 1).

Therapies that decrease androgen production from both endocrine and autocrine sources are also being developed. Abiraterone acetate is a selective and irreversible inhibitor of cytochrome P450 (CYP450)c17, an enzyme involved in androgen synthesis from both adrenal and other sources. Encouraging activity and safety with abiraterone were seen in phase I studies [11, 12]. In a phase II trial of 47 patients with CRPC with prior docetaxel therapy, 50% PSA declines were achieved with abiraterone in 51% of patients, and among the 30 patients who had RECIST-evaluable tumors, 27% had a PR [13]. In a phase II study of abiraterone plus prednisone in patients with CRPC and prior chemotherapy failure (n = 58), 50% PSA declines occurred in 55% of patients who were ketoconazole naïve, versus 30% of those who had received prior ketoconazole, and the median times to PSA progression were 198 days and 99 days, respectively [14]. Also, in a study of abiraterone plus prednisone in patients without prior chemotherapy or ketoconazole treatment (n = 33), a 50% PSA decline was achieved by 79% of patients and the median time to PSA progression was 71 weeks [15]. In a phase III randomized, double-blind, placebo-controlled trial of 1,195 metastatic CRPC patients previously treated with docetaxel, abiraterone plus prednisone led to a longer overall survival time than with treatment with prednisone plus placebo (median overall survival time, 14.8 versus 10.9 months; hazard ratio [HR], 0.65; p < .0001) [16]. A second phase III trial of abiraterone in asymptomatic or mildly symptomatic men with metastatic CRPC who had not received prior chemotherapy has completed accrual, with final results pending data maturity (Table 1).

TAK-700 is a novel CYP450c17 inhibitor similar to abiraterone. In preliminary data from a phase I/II study in patients with asymptomatic metastatic CRPC, TAK-700 was well tolerated and preliminary evidence of activity was seen, including 50% PSA declines in 12 of 15 patients who received doses ≥300 mg twice daily for ≥3 months [17]. Conversion of testosterone to the more potent DHT by 5α-reductase can occur within tumor tissue and is a mechanism for continued AR activation. Dutasteride, a dual-isofrom 5α-reductase inhibitor, was evaluated in several phase II trials. In a study of 25 evaluable patients with asymptomatic CRPC, two had a confirmed 50% PSA decline and nine had stable disease (SD) for 2.5–9 months (defined by PSA, RECIST, bone scan, and symptomatic criteria) [18]. Dutasteride plus ketoconazole and hydrocortisone was also studied in 57 patients with CRPC, resulting in a 50% PSA response in 56% of patients and median time to progression (TTP) of 14.5 months [19]. If antitumor effects are to be seen with dutasteride, it is likely that a dose >0.5 mg/day used in benign prostatic hypertrophy will be required.

Paradoxically, preclinical studies have shown that testosterone, if given at a high enough dose, caused regression of an androgen-independent prostate cancer cell line [20]. In a prior phase I trial of exogenous testosterone administered at three times the normal dose to 12 men with CRPC, treatment was well tolerated, and a >50% PSA decline was observed in one patient [21]. In order to block peripheral conversion to DHT and potentially increase serum testosterone levels and the therapeutic effect, dutasteride was added to high-dose exogenous testosterone and is currently being studied in an ongoing phase II trial.

HE3235, a structurally related synthetic analog of androstenediol, an adrenal androgen, has shown preclinical activity against CRPC cells and xenografts. In preclinical models of LNCaP cell lines exposed to the combination of HE3235 and either DHT or androstenediol, there was greater AR activity and PSA expression. Paradoxically, however, the addition of HE3235 led to inhibition of tumor formation/growth in xenograft studies, likely through inducing a proapoptotic effect on tumor cells [22]. Phase I studies have determined that HE3235 is well tolerated across a range of doses, and phase II studies are under way [23].

**Targeting Non–AR-Mediated Signaling**

In addition to AR-mediated pathways, evidence suggests that several alternative signaling pathways may also be involved in prostate cancer disease progression. Whether or
| Target | Agent | Phase | Design | Population | Primary endpoint | Estimated n of patients | ClinicalTrials.gov identifier |
|--------|-------|-------|--------|------------|------------------|-------------------------|-----------------------------|
| Androgen synthesis (CYP17) | Abiraterone and prednisone | III | Randomized, placebo controlled | Metastatic CRPC after docetaxel failure | OS | 1,158 | NCT00638690 |
| Androgen synthesis (CYP17) | Abiraterone and prednisone | III | Randomized, placebo controlled | Asymptomatic or mildly symptomatic CRPC | OS, PFS | 1,000 | NCT00887198 |
| Androgen synthesis (CYP17) | Abiraterone and prednisone | II | Single arm | Metastatic CRPC | Hormonal effects | 60 | NCT00544440 |
| TAK-700 | Abiraterone and prednisone | III | Randomized, placebo controlled | Metastatic CRPC | OS, PFS | 1,000 | NCT00887198 |
| TAK-700 | Abiraterone and prednisone | II | Single arm | Chemo-therapy-naïve nonmetastatic CRPC | PSA | 42 | NCT01046916 |
| TAK-700 plus docetaxel and prednisone | Abiraterone and prednisone | I/II | Dose ranging | Chemo-therapy-naïve metastatic CRPC | Safety | 100 | NCT00569153 |
| 5α-reductase | Dutasteride plus testosterone | II | Single arm | Metastatic CRPC | PFS | 30 | NCT00853697 |
| Androgen analog (androstenediol) | Dutasteride plus testosterone | II | Single arm | Metastatic CRPC after taxane failure | Safety, PK, activity | 122 | NCT00716794 |
| Androgen receptor | MDV3100 | III | Randomized, placebo controlled | CRPC after docetaxel failure | OS | 1,200 | NCT00974311 |
| Androgen receptor | MDV3100 | III | Randomized, placebo controlled | Chemo-therapy-naïve metastatic CRPC | OS, PFS | 1,680 | NCT01212991 |
| BCL-2, BCL-XL, MCL-1 | AT-101 and docetaxel | II | Randomized, placebo controlled | Chemo-therapy-naïve metastatic CRPC | OS | 220 | NCT00571675 |
| Clusterin (chaperone protein) | Custirsen plus docetaxel and prednisone | III | Randomized, placebo controlled | Chemo-therapy-naïve metastatic CRPC | OS | 800 | (Planned) |
| Clusterin (chaperone protein) | Custirsen plus docetaxel and prednisone | III | Randomized, placebo controlled | Metastatic CRPC after docetaxel failure | Pain palliation | 292 | NCT01083615 |
| CTLA-4 | Ipilimumab | III | Randomized, placebo controlled | Metastatic CRPC after docetaxel failure | OS | 800 | NCT00861614 |
| CTLA-4 | Ipilimumab | III | Randomized, placebo controlled | Asymptomatic or mildly symptomatic CRPC | OS | 600 | NCT01137810 |
| Endothelin A receptor | Atrasentan plus docetaxel and prednisone | III | Randomized, placebo controlled | Chemo-therapy-naïve metastatic CRPC | OS, PFS | 930 | NCT00134056 |
| Endothelin A receptor | Zibotentan | III | Randomized, placebo controlled | Chemo-therapy-naïve nonmetastatic CRPC | OS, PFS | 1,500 | NCT00626548 |
| Endothelin A receptor | Zibotentan | III | Randomized, placebo controlled | Asymptomatic or mildly symptomatic CRPC with bone metastases | OS | 848 | NCT00554229 |
| Endothelin A receptor | Zibotentan plus docetaxel | III | Randomized, placebo controlled | Chemo-therapy-naïve metastatic CRPC | OS | 1,445 | NCT00617669 |
| IGF-1R | Cixutumumab plus mitoxantrone and prednisone | II | Randomized, open label versus IMC-1121B | Metastatic CRPC after failure on docetaxel-based chemotherapy | PFS | 132 | NCT00638475 |
| IGF-1R | Figitumumab plus docetaxel and prednisone | II | Single arm | Chemo-therapy-naïve or docetaxel-refractory CRPC | PSA, tumor response | 120 | NCT00313781 |
| IGF-1R, mTOR | Cixutumumab plus temsirolimus | I/II | Single arm | Chemo-therapy-naïve metastatic CRPC | Tumor response, time to progression | 48 | NCT01026623 |
| mTOR | Everolimus | II | Single arm | Metastatic or locally advanced CRPC that is not progressing rapidly | PFS | 39 | NCT00976555 |
| mTOR | Everolimus plus docetaxel and prednisone | II | Single arm | Metastatic CRPC | Safety, tumor response | 60 | NCT00459186 |
| mTOR | Everolimus plus bicalutamide | II | Randomized, placebo controlled | Metastatic or recurrent CRPC | PSA response | 80 | NCT00814788 |
| mTOR | Everolimus | II | Molecular, genetic, and genomic assessments of mTOR inhibition | Metastatic CRPC | mTOR inhibition | 60 | NCT00636090 |
| mTOR | Temsirolimus | II | Single arm | Chemo-therapy-naïve CRPC | Tumor response | 24 | NCT00919035 |
| mTOR | Ridaforolimus plus bicalutamide | II | Randomized, placebo controlled | Asymptomatic metastatic CRPC | PSA response, dose-limiting toxicities | 156 | NCT00777959 |
not these pathways are truly independent of the AR or downstream components of AR signaling has not been fully elucidated, but this may vary by pathway. Several pathways that are a current focus for research with targeted agents are discussed below (Fig. 2).

**Src Pathway**

Src and other members of the Src-family kinases (SFKs) are nonreceptor tyrosine kinases that transduce signals from a range of upstream proteins, including receptors for epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) [24]. In addition to the established role of growth factor receptors in prostate cancer oncogenesis, preclinical studies have shown that Src and SFKs are highly active and/or overexpressed during prostate tumor growth and metastasis [25]. Src is also required during osteoclast functioning [26]. In a recent study of tumor samples from patients with CRPC, SFK activity was elevated in approximately 30% of cases and patients with greater SFK activity had a significantly shorter overall survival duration [27].

Dasatinib is a potent inhibitor of Src and SFKs that has shown preclinical antitumor and antimetastatic activity against prostate cancer cells and antosteoclast activity [28–31]. In a phase II trial of dasatinib monotherapy in 47 patients with metastatic chemotherapy-naive CRPC, 6% had a 50% reduction in PSA, 12 of 23 patients (52%) with RECIST-evaluable disease had SD, and 23 of 41 patients (49%) with bone metastases at baseline had no new bone lesions at week 12 [32]. In a phase I/II study of dasatinib plus docetaxel and prednisone in chemotherapy-naive patients with CRPC, 49% had a 50% PSA decline and 58% of

| Table 1. (Continued) |
|----------------------|
| Target | Agent | Phase | Design | Population | Primary endpoint | Estimated n of patients | ClinicalTrials.gov identifier |
| mTOR, VEGF | Temsirolimus plus bevacizumab | I/II | Dose ranging | Metastatic CRPC after chemotherapy failure | MTD, composite response | 34 | NCT01083368 |
| RANKL | Denosumab | III | Randomized, placebo controlled versus zoledronic acid | CRPC with bone metastases | Time to skeletal-related event | 1,904 | NCT00321620 |
| Denosumab | III | Randomized, placebo controlled | Nonmetastatic CRPC | Time to bone metastasis | 1,435 | NCT00286091 |
| Src | Dasatinib plus docetaxel and prednisone | III | Randomized, placebo controlled | Chemotherapy-naive metastatic CRPC | OS | 1,380 | NCT00744497 |
| Dasatinib or nilotinamide | II | Genomic-guided therapy | Metastatic CRPC | PFS | 60 | NCT00918385 |
| Saracatinib | II | Randomized versus zoledronic acid | Recurrent or progressive prostate or breast cancer with bone metastases | Bone markers | 132 | NCT00558272 |
| VEGF | Bevacizumab plus docetaxel and prednisone | III | Randomized, placebo controlled | Chemotherapy-naive CRPC | OS | 1,020 | NCT00110214 |
| Bevacizumab plus lenalidomide plus docetaxel and prednisone | II | Single arm | Metastatic chemotherapy-naive CRPC | Safety | 57 | NCT00942578 |
| Aflibercept (VEGF trap) plus docetaxel and prednisone | III | Randomized, placebo controlled | Metastatic chemotherapy-naive CRPC | OS | 1,200 | NCT00519285 |
| VEGFR | Cediranib | II | Single arm | Metastatic chemotherapy-naive CRPC after docetaxel failure | PFS | 62 | NCT00436956 |
| Cediranib plus docetaxel and prednisone | II | Randomized versus docetaxel/prednisone | Chemotherapy-naive CRPC | PFS | 104 | NCT00527124 |
| VEGFR, PDGFR, Kit | Sunitinib plus prednisone | III | Randomized, placebo controlled versus prednisone | Metastatic CRPC after docetaxel failure | OS | 819 | NCT00676650 |
| Sunitinib | II | Single arm | Metastatic CRPC after docetaxel failure | PFS | 50 | NCT00748358 |
| VEGFR, PDGFR, RAF, Kit | Sorafenib plus docetaxel | II | Single arm | Metastatic chemotherapy-naive CRPC | PSA response | 69 | NCT00589420 |

Abbreviations: BCL, B-cell lymphoma; CTLA-4, cytotoxic T-lymphocyte antigen 4; CRPC, castration-resistant prostate cancer; CYP, cytochrome P450; IGF-1R, insulin-like growth factor-1 receptor; MCL-1, myeloid cell leukemia sequence 1; MTD, maximum-tolerated dose; mTOR, mammalian target of rapamycin; OS, overall survival; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; PK, pharmacokinetics; PSA, prostate-specific antigen; RANKL, receptor activator for nuclear factor κB ligand; VEGFR, vascular endothelial growth factor receptor.
evaluable patients had a RECIST PR. Bone scans showed a reduction in the size and/or number of lesions in 28% of patients and no new lesions in 69% of patients [33]. These findings led to a randomized, placebo-controlled phase III trial of dasatinib plus docetaxel.

Saracatinib (AZD0530) is another oral Src inhibitor in clinical development. In preclinical studies, saracatinib blocked proliferation and migration in a range of prostate cancer cell lines, including androgen-independent xenografts [34–36]. Saracatinib has also shown antisteoelast activity in vitro and in vivo [37, 38]. In an initial phase II, single-arm, Simon two-stage trial of saracatinib monotherapy in patients with advanced CRPC, five of 28 patients had a slight decline in PSA, though no patient achieved a 30% decline. The median progression-free survival interval was 8 weeks [39].

Phosphoinositide-3-Kinase–Akt–Mammalian Target of Rapamycin Pathway

Upregulation of the phosphoinositide-3-kinase (PI3K)–Akt–mammalian target of rapamycin (mTOR) pathway has been detected in various tumors, including prostate cancer [40]. PI3K is activated by several extracellular receptors, including EGF receptor and insulin-like growth factor-1 receptor (IGF-1R), in addition to intracellular oncogenes such as RAS [41]. In turn, activated PI3K induces Akt to phosphorylate and activate mTOR, which promotes cell division. PI3K activation is regulated by tumor suppressor phosphatase and tensin homolog (PTEN), and loss of PTEN function has been detected in prostate cancer [42–44]. Preclinical studies suggest that loss of PTEN function and/or activation of the PI3K–Akt–mTOR pathway can result in androgen-independent prostate cancer growth [45, 46]. Furthermore, deletion of PTEN has been associated with earlier disease progression in patients with prostate cancer [47, 48] and greater AR expression and cancer-associated mortality in patients with CRPC [49].

Several mTOR inhibitors have been developed. In mouse studies, everolimus (RAD001) inhibited the growth of prostate cancer cells in bone and effects were augmented by combination treatment with docetaxel and zoledronic acid [50]. In a phase I dose-escalation trial of everolimus plus docetaxel in chemotherapy-naïve patients with metastatic CRPC, 50% PSA declines were seen in 10 of 12 patients [52]. In a phase II,
single-arm, Simon two-stage study of everolimus mono-
therapy in 19 patients with CRPC, most of whom were do-
cetaxel refractory, the median TTP was 85 days and no PSA
or tumor responses were recorded [53]. In preclinical studies,
temsirolimus (CCI-779) inhibited the growth of pros-
tate cancer cell lines and xenografts, and had greater activity in combination with docetaxel [54, 55]. In addition, phase I studies of ridaforolimus (AP23573) in patients with advanced solid tumors have successfully been completed [56, 57]. A single-arm, phase II trial of ridaforolimus mono-
therapy in taxane-resistant CRPC patients has completed enrollment and results are pending (ClinicalTrials.gov Identifier, NCT00110188). Clinical studies with everoli-
mus, temsirolimus, and ridaforolimus in CRPC are summa-
rized in Table 1.

Chaperone Proteins
Chaperone (heat-shock) proteins have antiapoptotic prop-
erties and are an established target for anticancer therapy. Although heat-shock protein 90 (HSP90) was an early fo-
cus for study, no HSP90 inhibitor has so far proved to be therapeutically viable for prostate cancer, although work is ongoing [58]. Clusterin, an alternative chaperone protein, is a novel target. In prostate cancer cell lines, clusterin over-
expression resulted in androgen-independent growth [59] and clusterin gene silencing induced apoptosis and signifi-
cantly reduced growth [60]. Clusterin expression is upregu-
lated in patients with prostate cancer who have received androgen-deprivation therapy (ADT) [61].

Custirsen (OGX-011) is an antisense inhibitor of clus-
terin that suppresses clusterin expression in tumor tissue
when administered to patients with localized prostate can-
cer [62]. In vitro, custirsen was found to resensitize do-
cetaxel-refractory prostate cancer cell lines to docetaxel
[63]. A randomized phase II study of docetaxel plus predniso-
one with or without custirsen in patients with metastatic
CRPC (n = 82) has been completed, and showed a longer median overall survival time in the custirsen arm (24 months versus 17 months; HR, 0.61; p = .06), although rates of PSA and tumor response were similar [64]. Based on these findings, phase III trials of OGX-011 plus do-
cetaxel and prednisone are planned.

IGF-1R Pathway
IGF-1R has antiapoptotic and transforming activities, and
IGF-1R–mediated signaling can be detected during several stages of metastasis, including adhesion, migration, and in-
vasion [65]. In vitro models suggest that increased IGF-1R
expression in prostate cancer cells can lead to androgen in-
dependence [66, 67]. In a recent study using frozen tissue
specimens, IGF-1R was more frequently expressed in stro-
mal tissue surrounding malignant than surrounding nonma-
lignant tissue and in high-grade than in low-grade tumors
[68]. Studies of IGF-1R ligands have provided further evi-
dence for the oncogenic role of IGF signaling. In transgenic
mice expressing human IGF-1 in the basal prostate epithe-
lium, spontaneous tumorigenesis was seen [69]. In a study of prostatic tumor tissue, expression of IGF-1 and IGF-2
was higher in high-grade than in low-grade tumors [70].
Furthermore, in a meta-analysis of clinical studies, elevated circulating concentrations of IGF-1 were associated with a greater risk for prostate cancer [71].

Three monoclonal antibodies against IGF-1R, cixutu-
mumab (IMC-A12), figitumumab (CP-751,871), and
AMG-479, are being assessed in CRPC patients and have demonstrated good tolerability in phase I studies [72–75].
In a phase II study of cixutumumab in men with asymptom-
atic metastatic CRPC, nine of 31 patients achieved SD for
≥6 months (range, 7.4–12.5 months) [76]. Further studies
of IGF-1R antibodies are in progress (Table 1). The develop-
ment of figitumumab was suspended after an unexpected
finding of a higher treatment-related mortality rate when
this agent was added to standard chemotherapy.

VEGF
VEGF, stimulated by such factors as hypoxia, low pH, and
growth factor receptors, plays a key role in promoting an-
giogenesis and tumor progression in various tumor types.
VEGF expression has been found in both localized and me-
 metastatic prostate cancer specimens, and higher plasma VEGF
levels have been correlated with disease severity [77] In preclinical models, antibodies directed against VEGF in-
hhibited the growth of prostate cancer tumors [78].

Bevacizumab, a humanized monoclonal antibody di-
rected against VEGF, has been evaluated in prostate cancer
in several clinical trials. In a phase II trial of 15 patients
with CRPC, after 12 weeks of therapy with bevacizumab dosed
at 10 mg/kg every 2 weeks, no patients experienced an ob-
jective response or PSA decline >50% [79]. In a random-
ized, double-blind, placebo-controlled phase III trial of
docetaxel plus prednisone with or without bevacizumab in
1,050 men with chemotherapy-naïve CRPC, the median
overall survival time was not significantly longer with the addition of bevacizumab; however, the median progres-
sive-free survival interval was longer—7.5 months in the
control arm and 9.9 months in the bevacizumab-containing
arm (stratified log-rank p-value <.0001) [80].

Aflibercept, a VEGF trap consisting of the Fc portion of
human IgG1 fused to the extracellular ligand-binding do-
main of VEGF receptor (VEGFR)-1 and VEGFR-2, is cur-
rently being evaluated in a placebo-controlled, randomized
phase III trial in combination with docetaxel plus prednisone (ClinicalTrials.gov Identifier, NCT00519285).

Sunitinib, a small molecular tyrosine kinase inhibitor of VEGFR-1 to VEGFR-3, along with multiple other receptors including PDGF receptor (PDGFR)-α and PDGFR-β, inhibits angiogenesis and has shown promising activity in prostate cancer, especially in the postdocetaxel setting. In a single-arm, phase II trial of sunitinib in 36 men with metastatic CRPC previously treated with docetaxel, seven patients (21.2%) had a PSA decline >30% and two patients had an objective response [81]. A phase III trial, however, of sunitinib plus prednisone versus placebo plus prednisone, in men with CRPC and prior docetaxel and with a primary endpoint of overall survival, was terminated prematurely as a result of futility in September 2010 (ClinicalTrials.gov Identifier, NCT00676650).

**Endothelin**

The endothelin family of peptides, mediated mostly by endothelin-1 binding to the endothelin-A receptor, modulates vasomotor tone, nociception, and cellular proliferation in a variety of tissues [82]. Endothelin-1 acts via the endothelin-A receptor to promote prostate cancer progression via several mechanisms, including acting as a mitogen for both prostate cancer cells and osteoblasts, which are responsible for the osteoblastic metastatic lesions common in metastatic prostate cancer [83, 84]. Selective endothelin-A receptor antagonists block the proliferation of prostate cancer cells and osteoblasts in the presence of exogenous endothelin [84].

Atrasentan is a potent and highly selective inhibitor of the endothelin-A receptor, and was shown in a randomized phase II trial, at a dose of 10 mg/day, to produce a trend towards a longer TTP than with placebo in a study of 288 men with metastatic CRPC (median TTP, 183 days versus 137 days; p = .13) [85]. However, two subsequent, randomized, placebo-controlled, phase III trials of men with either metastatic or metastatic CRPC failed to demonstrate a significantly longer time to disease progression in patients treated with atrasentan than in those treated with placebo [86, 87]. A randomized phase III trial comparing prednisone plus docetaxel with or without atrasentan has finished accrual, with final results pending (ClinicalTrials.gov Identifier, NCT00134056).

Zibotentan is a nonpeptide, orally bioavailable selective inhibitor of endothelin-A receptor that was well tolerated in a phase I trial, with a maximum-tolerated dose of 15 mg/day [88]. In a randomized, phase II trial with three treatment arms consisting of men with metastatic CRPC treated with zibotentan 10 mg/day, zibotentan 15 mg/day, or placebo, the primary endpoint of a longer time to disease progression was not significant; however, there was a trend toward longer overall survival in both zibotentan arms, compared with placebo, with a median follow-up of 22 months (HR, 0.76; p = .103 for the 15-mg arm. HR, 0.83; p = .254 for the 10-mg arm) [89]. Based on these results, three phase III trials of zibotentan in men with CRPC are ongoing (Table 1).

**INDIVIDUALIZED TARGETED THERAPY FOR CRPC**

**Individual Tumor Gene/Protein Expression to Guide Therapy**

Because of biological heterogeneity, including the potential for continuing AR-mediated signaling or androgen independence, it is likely that no single agent will be uniformly effective for treating CRPC. This hypothesis is supported by the variable efficacy observed in clinical trials of the selected novel agents outlined above. A more individualized and arguably more rational approach to treatment is currently being investigated in CRPC, which involves using genomic and proteomic analyses to assess the involvement of specific molecular pathways. The aim is to tailor treatment based on individual tumor characteristics and thereby select patients who are most likely to respond to different therapies. The benefits of individualized therapy have already been demonstrated in other tumor types, particularly in breast cancer using human epidermal growth factor receptor 2 testing and trastuzumab therapy. Predictive markers of response to secondary hormonal therapy in CRPC have already been identified. For example, CRPC tumors with AR gene amplification respond better to secondary hormone therapy (combined androgen blockade) than tumors without AR amplification [90].

Recent studies in CRPC have further evaluated a genomic-guided approach to treatment [91]. Using an androgen-sensitive prostate cancer cell line (LNCaP), a transcription signature for AR activity was identified, which was confirmed to be robust in independent data sets of prostate cancer cell lines and human tumors. When the AR signature was investigated in patient samples, AR activity was generally higher in localized, untreated tumors and lower after neoadjuvant hormone therapy and in CRPC, seemingly representing declining AR activity with prostate cancer progression. However, AR activity was heterogeneous in CRPC patients, with approximately one third of patient samples showing persistent AR activity, which could help to explain the variable responses to AR-directed therapies observed in trials. To identify novel therapeutic options that may be most useful for patients with low AR activity, samples were compared with published signatures for other molecular targets [91–93]. Of those tested, the signature for Src activity most consistently correlated with low AR activity, both in localized (p = .0071) and metastatic (p = .0033) disease. Similarly, low AR activity correlated with a signal predicting sensitivity to the Src inhibitor dasatinib (p = .019).
These findings suggest that patients with CRPC who have low AR activity detected in tumor samples might benefit more from Src inhibitor treatment than AR-directed therapy.

A prospective study is now in progress to test a genomic-guided approach to treatment (ClinicalTrials.gov Identifier, NCT00918385). Patients with metastatic CRPC will be prescreened and those with tumors with high AR activity will receive nilutamide, an AR-targeted agent, whereas those with low AR activity will be treated with dasatinib. Patients failing single-agent treatment will receive combination therapy. A study is also being performed with everolimus that will examine gene expression profiles and molecular characteristics in patients with CRPC to determine any possible association with treatment responses, which could potentially inform a future genomic-guided trial (ClinicalTrials.gov Identifier, NCT00636090).

A key question in the development of genomic-guided clinical trials centers around the type of specimen that is used to molecularly define an individual patient’s tumor. Prior comprehensive gene expression analyses that compared localized prostate cancers with metastatic tumors found wide variability in the expression of various subsets of genes, including those involved in cell cycling, cell adhesion, and signal transduction [94]. Given the molecular heterogeneity of prostate cancer, there has been considerable interest in developing techniques to molecularly characterize metastatic prostate cancer tissue rather than specimens obtained from prior prostate biopsies or prostatectomy specimens containing localized prostate cancer. In the aforementioned phase II trial of nilutamide and dasatinib (ClinicalTrials.gov Identifier, NCT00918385), fresh tissue obtained via biopsy of a metastatic site will be used to molecularly characterize a patient’s tumor.

Circulating tumor cells (CTCs) potentially represent an alternative, less invasive means to obtain gene expression data. Techniques to identify and isolate these cells with increasing sensitivity and purity are actively being refined [95]. Enumeration of the number of CTCs pre- and postinitiation of chemotherapy was shown to be predictive of overall survival in a prospective study [96]. Needed, however, are refinements in techniques used to not only count, but also to characterize, CTC gene expression profiles, as well as studies that compare molecular profiles among CTCs, primary tumor samples, and metastatic sites within individual patients to assess for concordancy (or lack thereof) in gene expression over time and location.

**Pharmacogenetic Profiling**

Recent data have established that pharmacogenomic factors, that is, genetic polymorphisms affecting proteins involved in drug metabolism or action, may play a role in determining response to targeted therapies, both in prostate cancer and other solid tumors. For example, among 529 patients undergoing ADT, polymorphisms in three separate genes involved in hormone synthesis (CYP19A1, HSD3B1, and HSD17B4) were significantly (p < .01) associated with a longer TTP, and best responses were observed in patients with more than one polymorphism [97]. Furthermore, survival on docetaxel in patients with CRPC has been associated with specific genotypes of ABCB1 (encoding a drug efflux protein) and CYP1B1 (encoding an enzyme involved in estrogen metabolism) [98, 99]. Tailoring therapy based on pharmacogenomic parameters is likely to be tested in future prospective studies.

**CONCLUSIONS**

Traditional drug discovery methods have identified several potential molecular targets for treating CRPC, including those that inhibit AR-mediated and non–AR-mediated signaling. In recent years, novel agents have shown promise in clinical trials, including agents targeting the androgen axis (e.g., novel AR antagonists and inhibitors of androgen production) and agents with other targets (e.g., Src, IGF-1R, mTOR, and cluseterin). However, it is becoming increasingly apparent that CRPC is a heterogeneous disease and patient subgroups are likely to exist that are characterized by the involvement of different signaling pathways in disease progression to different degrees. This suggests that a more rational/individualized approach is required to maximize potential benefits from targeted therapy. Using genomic signatures, a recent study showed that patients with low AR activity are more likely to have high Src activity and sensitivity to dasatinib, and an ongoing study will provide an initial test of whether genomic-guided treatment can increase response rates. Identifying patient populations with a specific molecular subtype should hopefully improve the chances of treatment response, and ultimately, a scenario could be envisaged in which patients receive personalized targeted therapy based on their genomic profile, using both the “real-time” tumor genotype/phenotype and the pharmacogenetic profile of the patient. Discoveries in CRPC could translate to other advanced cancers.

**AUTHOR CONTRIBUTIONS**

Conception/Design: Rahul Aggarwal, Charles J. Ryan
Data analysis and interpretation: Rahul Aggarwal, Charles J. Ryan
Manuscript writing: Rahul Aggarwal, Charles J. Ryan
Final approval of manuscript: Rahul Aggarwal, Charles J. Ryan

The authors take full responsibility for the content of this publication but thank Jeremy Gardner, Ph.D. (StemScientific), funded by Bristol-Myers Squibb, for providing assistance with copyediting, literature searching, and figure/table preparation. Bristol-Myers Squibb did not influence the content of the manuscript, nor did the authors receive financial compensation.
REFERENCES

1. Tannock IF, de Wit R, Berry WR et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–1512.

2. Petrylak DP, Tangen CM, Hussain MH et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004;351:1513–1520.

3. Attard RM, Takimoto CH, Gottardis MM. Castration-resistant prostate cancer: Locking up the molecular escape routes. Clin Cancer Res 2009;15:3251–3255.

4. Chen Y, Sawyers CL, Scher HI. Targeting the androgen receptor pathway in prostate cancer. Curr Opin Pharmacol 2008;8:440–448.

5. Chen CD, Welsbie DS, Tran C et al. Molecular determinants of resistance to antiandrogen therapy. Nat Med 2004;10:33–39.

6. Small EJ, Halabi S, Dawson NA et al. Antiandrogen withdrawal alone or in combination with ketoconazole in androgen-independent prostate cancer patients: A phase III trial (CALGB 9583). J Clin Oncol 2004;22:1025–1033.

7. Sartor AO, Tangen CM, Hussain MH et al. Antiandrogen withdrawal in castrate-refractory prostate cancer: A Southwest Oncology Group trial (SWOG 9426). Cancer 2008;112:2393–2400.

8. Samson DJ, Seidenfeld J, Schmitt B et al. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. Cancer 2002;95:361–376.

9. Tran C, Ouk S, Clegg NJ et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009;324:787–790.

10. Scher HI, Beer TM, Higano CS et al. Antitumour activity of MDV3100 in castration-resistant prostate cancer: A phase 1–2 study. Lancet 2010;375:1437–1446.

11. Attard G, Reid AH, Yap TA et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. J Clin Oncol 2008;26:4563–4571.

12. Ryan CJ, Smith MR, Feng L et al. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. J Clin Oncol 2010;28:1481–1488.

13. Reid AH, Attard G, Danila DC et al. Significant and sustained antitumor activity in post-docetaxel, castration-resistant prostate cancer with the CYP17 inhibitor abiraterone acetate. J Clin Oncol 2010;28:1489–1495.

14. Danila DC, Morris MJ, de Bono JS et al. Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated castration-resistant prostate cancer. J Clin Oncol 2010;28:1496–1501.

15. Ryan CJ, Smith MR, Logothetis C et al. Median time to progression in chemotherapy-naive patients with castration-resistant prostate cancer treated with abiraterone acetate and low-dose prednisone [abstract 4671]. J Clin Oncol 2010;28(15 suppl):384s.

16. de Bono JS, Logothetis CJ, Fizazi K et al. Abiraterone acetate (AA) plus low dose prednisone (P) improves overall survival (OS) in patients (Pts) with metastatic castration resistant prostate cancer (mCRPC) who have progressed after docetaxel-based chemotherapy: Results of COU-AA-301, a randomized double-blind placebo-controlled phase III study. Ann Oncol 2010;21(suppl 5):LBA5.

17. Dreier C, Agus DB, MacVicar GR et al. Safety, pharmacokinetics, and efficacy of TAK-700 in metastatic castration-resistant prostate cancer: A phase I/II, open-label study [abstract 3084]. J Clin Oncol 2010;28(15 suppl):254s.

18. Shah SK, Trump DL, Sartor O et al. Phase II study of datatanter for recurrent prostate cancer during androgen deprivation therapy. J Urol 2009;181:621–626.

19. Taplin ME, Regan MM, Ko YJ et al. Phase II study of androgen synthesis inhibition with ketoconazole, hydrocortisone, and dutasteride in asymptomatic castration-resistant prostate cancer. Clin Cancer Res 2009;15:7099–7105.

20. Kokontis JM, Hay N, Liao S. Progression of LNCaP prostate tumor cells during androgen deprivation: Hormone-independent growth, repression of proliferation by androgen, and role for p27Kip1 in androgen-induced cell cycle arrest. Mol Endocrinol 1998;12:941–953.

21. Morris MJ, Huang D, Kelly WK et al. Phase I trial of high-dose exogenous testosterone in patients with castration-resistant metastatic prostate cancer. Eur Urol 2009;56:237–244.

22. Trauger R, Corey E, Bell D et al. Inhibition of androstenediol-dependent LNCaP tumour growth by 17α-ethyl-5α-androstan-3α, 17β-diol (HE3235). Br J Cancer 2009;100:1068–1072.

23. Montgomery RB, Morris MJ, Ryan CJ et al. HE3235, a synthetic adrenal hormone disease-modifying agent, in castrate resistant prostate cancer: Results of phase II/III clinical trial [abstract 4674]. J Clin Oncol 2010;28(15 suppl):385s.

24. Chang YM, Kung HJ Evans CP. Nonreceptor tyrosine kinases in prostate cancer. Neoplasia 2007;9:90–100.

25. Fizazi K. The role of Src in prostate cancer. Ann Oncol 2007;18:1765–1773.

26. Araujo J, Logothetis C. Targeting Src signaling in metastatic bone disease. Int J Cancer 2009;124:1–6.

27. Tatarov O, Mitchell TJ, Seywright M et al. SRC family kinase activity is up-regulated in hormone-refractory prostate cancer. Clin Cancer Res 2009;15:3540–3549.

28. Nana S, Kim D, Cheng JQ et al. Action of the Src family kinase inhibitor, dasatinib (BMS-354825), on human prostate cancer cells. Cancer Res 2005;65:9185–9189.

29. Park SI, Zhang J, Phillips KA et al. Targeting SRC family kinases inhibits growth and lymph node metastases of prostate cancer in an orthotopic nude mouse model. Cancer Res 2008;68:3323–3333.

30. Koreckij T, Nguyen H, Brown LG et al. Dasatinib inhibits the growth of prostate cancer in bone and provides additional protection from osteolysis. Br J Cancer 2009;101:263–268.

31. Vandyke K, Dewar AL, Farrugia AN et al. Dasatinib (BMS-354825), on human prostate cancer cells. Cancer Res 2008;68:3323–3333.

32. Yokoyama, Ryan
in a new neuropeptide-autocline model of androgen-insensitive prostate cancer. Cancer Res 2009;69:151–160.

37 de Vries TJ, Mullender MG, van Duin MA et al. The Src inhibitor AZD0530 reversibly inhibits the formation and activity of human osteoclasts. Mol Cancer Res 2009;7:476–488.

38 Evans CP, Bai L, Kung H et al. Effect of the specific Src kinase inhibitor AZD0530 on osteolytic lesions in prostate cancer [abstract 170]. Presented at the 2008 American Society of Clinical Oncology Genitourinary Cancers Symposium, San Francisco, CA, February 14–16, 2008. Available at http://www.asco.org/ASCOv2/Meetings/Abstracts, accessed February 8, 2011.

39 Lara PN Jr, Longmate J, Evans CP et al. A phase II trial of the Src–kinase inhibitor AZD0530 in patients with advanced castration-resistant prostate cancer: A California Cancer Consortium study. Anticancer Drugs 2009;20:179–184.

40 Morgan TM, Koreckji TD, Corey E. Targeted therapy for advanced prostate cancer: Inhibition of the PI3K/Akt/mTOR pathway. Curr Cancer Drug Targets 2009;9:237–249.

41 LoPiccolo J, Blumenthal GM, Bernstein WB et al. Targeting the PTEN/MMAC1/TEP1 pathway: Effective combinations and clinical considerations. Drug Resist Updat 2008;11:32–50.

42 Cairns P, Okami K, Halachmi S et al. Frequent inactivation of PTEN/MMAC1 in primary prostate cancer. Cancer Res 1997;57:4997–5000.

43 Pesche S, Latil A, Muzeau F et al. PTEN/MMAC1 involvement in primary prostate cancers. Oncogene 1998;16:2879–2883.

44 Shen MM, bate-Shen C. Pten inactivation and the emergence of androgen-independent prostate cancer. Cancer Res 1999;59:4291–4296.

45 McMenamin ME, Soung P, Perera S et al. Loss of PTEN expression in paraffin-embedded primary prostate cancer correlates with high Gleason score and advanced stage. Cancer Res 1999;59:4291–4296.

46 Shen MM, bate-Shen C. Pten inactivation and the emergence of androgen-independent prostate cancer. Cancer Res 2007;67:6535–6538.

47 Jiao J, Wang S, Qiao R et al. Murine cell lines derived from Pten null prostate cancer show the critical role of PTEN in hormone refractory prostate cancer development. Cancer Res 2007;67:6083–6091.

48 Schmitz M, Grignard G, Margue C et al. Complete loss of PTEN expression as a possible early prognostic marker for prostate cancer metastasis. Int J Cancer 2007;120:1284–1292.

49 Yoshimoto M, Cunha IW, Coudry RA et al. FISH analysis of 107 prostate cancers shows that PTEN genomic deletion is associated with poor clinical outcome. Br J Cancer 2007;97:678–685.

50 Sircar K, Yoshimoto M, Monzon FA et al. PTEN genomic deletion is associated with p-Akt and AR signalling in poorer outcome, hormone refractory prostate cancer. J Pathol 2009;218:505–513.

51 Morgan TM, Pitts TE, Gross TS et al. RAD001 (everolimus) inhibits growth of prostate cancer in the bone and the inhibitory effects are increased by combination with docetaxel and zoledronic acid. Prostate 2008;68:861–871.

52 Ross RW, Beer TM, Jacobus S et al. A phase 2 study of carboplatin plus docetaxel in men with metastatic hormone-refractory prostate cancer who are refractory to docetaxel. Cancer 2008;112:521–526.

53 Gross ME, Soschia J, Sakowsky S et al. Phase I trial of RAD001, bevacizumab, and docetaxel for castration-resistant prostate cancer [abstract 5154]. J Clin Oncol 2009;27(15 suppl):272s.

54 George DJ, Armstrong AJ, Creel P et al. A phase II study of RAD001 in men with hormone-refractory metastatic prostate cancer (HRPC) [abstract 181]. Presented at the 2008 American Society of Clinical Oncology Genitourinary Cancers Symposium, San Francisco, CA, February 14–16, 2008. Available at http://www.asco.org/ASCOv2/Meetings/Abstracts, accessed February 8, 2011.

55 Wu L, Birle DC, Tannock IF. Effects of the mammalian target of rapamycin inhibitor CCI-779 used alone or with chemotherapy on human prostate cancer cells and xenografts. Cancer Res 2005;65:2825–2831.

56 Fung AS, Wu L, Tannock IF. Concurrent and sequential administration of chemotherapy and the mammalian target of rapamycin inhibitor temsirolimus in human cancer cells and xenografts. Clin Cancer Res 2009;15:5389–5395.

57 Mita MM, Mita AC, Chu QS et al. Phase I trial of the novel mammalian target of rapamycin inhibitor deforolimus (AP23573; MK-8669) administered intravenously daily for 5 days every 2 weeks to patients with advanced malignancies. J Clin Oncol 2008;26:361–367.

58 Hartford CM, Desai AA, Janisch L et al. A phase I trial to determine the safety, tolerability, and maximum tolerated dose of deforolimus in patients with advanced malignancies. Clin Cancer Res 2009;15:1428–1434.

59 Banerji U. Heat shock protein 90 as a drug target: Some like it hot. Curr Cancer Drug Targets 2009;9:14–19.

60 Miyake H, Nelson C, Rennie PS et al. Testosterone-repressed prostate message-2 is an antiapoptotic gene involved in progression to androgen independence in prostate cancer. Cancer Res 2000;60:170–176.

61 Trougakos IP, So A, Janssen B et al. Silencing expression of the clusterin/apolipoprotein J gene in human cancer cells using small interfering RNA induces spontaneous apoptosis, reduced growth ability, and cell sensitization to genotoxic and oxidative stress. Cancer Res 2004;64:1834–1842.

62 July LV, Akbari M, Zellweger T et al. Clusterin expression is significantly enhanced in prostate cancer cells following androgen withdrawal therapy. Prostate 2002;50:179–188.

63 Chi KN, Eisenhauer E, Fazli L et al. A phase I pharmacokinetic and pharmacodynamic study of OGX-011, a 2′-methoxyethyl antisense oligonucleotide to clusterin, in patients with localized prostate cancer. J Natl Cancer Inst 2005;97:1287–1296.

64 Sowery RD, Hadashka BA, So AI et al. Clusterin knockdown using the antisense oligonucleotide OGX-011 re-sensitizes docetaxel-refractory prostate cancer PC-3 cells to chemotherapy. BJU Int 2008;102:389–397.

65 Chi KN, Hotte SJ, Yu EY et al. Mature results of a randomized phase II study of OGX-011 in combination with docetaxel/prednisone versus docetaxel/prednisone in patients with metastatic castration-resistant prostate cancer [abstract 5012]. J Clin Oncol 2009;27(15 suppl):238s.

66 Werner H, Bruchim I. The insulin-like growth factor-I receptor as an oncogene. Arch Physiol Biochem 2009;115:58–71.

67 Nickerson T, Chang F, Lorimier D et al. In vivo progression of LAPC-9 and LNCaP prostate cancer models to androgen independence is associated with increased expression of insulin-like growth factor I (IGF-I) and IGF-I receptor (IGF-IR). Cancer Res 2001;61:134–140.

68 Knuecl SL, Sikes RA, Edlund NM et al. Increased insulin-like growth factor I receptor expression and signaling are components of androgen-independent progression in a lineage-derived prostate cancer progression model. Cancer Res 2004;64:8620–8629.

69 Ryan CJ, Haqq CM, Simko J et al. Expression of insulin-like growth factor-I receptor in local and metastatic prostate cancer. Urol Oncol 2007;25:134–140.

70 DiGiovanni J, Kiguchi K, Frijhoff A et al. Deregulated expression of insulin-like growth factor 1 in prostate epithelium leads to neoplasia in transgenic mice. Proc Natl Acad Sci U S A 2000;97:3455–3460.

71 Liao Y, Abel U, Grobholz R et al. Up-regulation of insulin-like growth factor axis components in human primary prostate cancer correlates with tumor grade. Hum Pathol 2005;36:1186–1196.

72 Renenh AG, Zwahlen M, Minder C et al. Insulin-like growth factor
(IGF)-1, IGF binding protein-3, and cancer risk: Systematic review and meta-regression analysis. Lancet 2004;363:1346–1353.

72 Lu D, Zhang H, Koo H et al. A fully human recombinant IgG-like bispecific antibody to both the epidermal growth factor receptor and the insulin-like growth factor receptor for enhanced antitumor activity. J Biol Chem 2005; 280:19665–19672.

73 Haluska P, Shaw HM, Batzel GN et al. Phase I dose escalation study of the anti-insulin-like growth factor-I receptor monoclonal antibody CP-751,871 in patients with refractory solid tumors. Clin Cancer Res 2007;13:5834–5840.

74 Higano CS, Yu EY, Whiting SH et al. A phase I, first in man study of weekly IMC-A12, a fully human insulin like growth factor-1 receptor IgG1 monoclonal antibody, in patients with advanced solid tumors [abstract 3505]. J Clin Oncol 2007;25(18 suppl):139.

75 Tolcher AW, Sarantopoulos J, Patnaik A et al. Phase I, pharmacokinetic, and pharmacodynamic study of AMG 479, a fully human monoclonal antibody to insulin-like growth factor receptor I. J Clin Oncol 2009;27:5800–5807.

76 Higano C, Alumkal J, Ryan CJ et al. A phase II study evaluating the efficacy and safety of single agent IMC A12, a monoclonal antibody, against the insulin-like growth factor-I receptor, as monotherapy in patients with metastatic, asymptomatic castration-resistant prostate cancer [abstract 5142]. J Clin Oncol 2009;27(27 suppl):269s.

77 Duque JL, Loughlin KR, Adam RM et al. Plasma levels of vascular endothelial growth factor are increased in patients with metastatic prostate cancer. Urology 1999;45:523–527.

78 Melnyk O, Zimmerman M, Kim KJ et al. Neutralizing anti-vascular endothelial growth factor antibody inhibits further growth of established prostate cancer and metastases in pre-clinical model. J Urol 1999;161:960–963.

79 Reese DM, Fratesi P, Corry M et al. A phase II trial of humanized anti-vascular endothelial growth factor antibody for the treatment of androgen-independent prostate cancer. Prostate 2001;3:65–70.

80 Kelly WK, Halabi S, Carducci MA et al. A randomized, double-blind, placebo-controlled phase III trial comparing docetaxel, prednisone, and placebo with docetaxel, prednisone, and bevacizumab in men with metastatic castration-resistant prostate cancer (mCRPC): Survival results of CALGB 90401. J Clin Oncol 2010;28(28 suppl):LBA4511.

81 Sonpavde G, Periman PO, Bernold D et al. Sunitinib malate for metastatic hormone-refractory prostate cancer: A randomized, phase II, placebo-controlled trial. J Clin Oncol 2003;21:679–689.

82 Nelson JB, Chin JL, Love W et al. Results of a phase 3 randomized controlled trial of the safety and efficacy of atrasentan in men with metastatic hormone-refractory prostate cancer. Cancer 2007;110:1959–1966.

83 Nelson JB, Hedican SP, George DJ et al. Identification of endothelin-1 in prostate cancer. Cancer 2007;110:1959–1966.

84 Nelson JB, Nguyen SH, Wu-Wong JR et al. New bone formation in an osteoblastic tumor model is increased by endothelin-1 overexpression and decreased by endothelin A receptor blockade. Urology 1999;53:1063–1069.

85 Carducci MA, Padley RJ, Bruel J et al. Effect of endothelin-A receptor blockade with atrasentan on tumor progression in men with hormone-refractor prostate cancer: A randomized, phase II, placebo-controlled trial. J Clin Oncol 2003;21:679–689.

86 Carducci MA, Saad F, Abrahamsson PA et al. A phase 3 randomized controlled trial of the efficacy and safety of atrasentan in men with metastatic hormone-refractory prostate cancer. Cancer 2007;110:1959–1966.

87 Nelson JB, Chin JL, Love W et al. Results of a phase 3 randomized controlled trial of the safety and efficacy of atrasentan in men with non-metastatic hormone-refractory prostate cancer (HRPC) [abstract 146]. Presented at the 2007 Prostate Cancer Symposium, Orlando, FL, February 22–24, 2007.

88 Schelman WR, Liu G, Wilding G et al. A phase I study of zibotentan (ZD4054) in patients with metastatic castrate-resistant prostate cancer. Invest New Drugs 2011;29:118–125.

89 James ND, Cayt A, Payne H et al. Final safety and efficacy analysis of the specific endothelin A receptor antagonist zibotentan (ZD4054) in patients with metastatic castration-resistant prostate cancer and bone metastases who were pain-free or mildly symptomatic for pain: A double-blind, placebo-controlled, randomized phase II trial. BJU Int 2010;106:966–973.

90 Palmberg C, Koivisto P, Kakkola L et al. Androgen receptor gene amplification at primary progression predicts response to combined androgen blockade as second line therapy for advanced prostate cancer. J Urol 2000;164:1992–1995.

91 Mendiratta P, Mostaghel E, Guinney J et al. Genomic strategy for targeting therapy in castration-resistant prostate cancer. J Clin Oncol 2009;27:2022–2029.

92 Bild AH, Yao G, Chang JT et al. Oncogenic pathway signatures in human cancers as a guide to targeted therapies. Nature 2006;439:353–357.

93 Wang XD, Reeves K, Luo FR et al. Identification of candidate predictive and surrogate molecular markers for dasatinib in prostate cancer: Rationale for patient selection and efficacy monitoring. Genome Biol 2007;8:R255.

94 La Tulippe E, Satagopan J, Smith A et al. Comprehensive gene expression analysis of prostate cancer reveals distinct transcriptional programs associated with metastatic disease. Cancer Res 2002;62:4499–4506.

95 Nagrath S, Sequist LV, Maheswaran S et al. Isolation of rare circulating tumour cells in cancer patients by microchip technology. Nature 2007;450:1235–1239.

96 de Bono JS, Scher HI, Montgomery RB et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. Clin Cancer Res 2008;14:6302–6309.

97 Ross RW, Oh WK, Xie W et al. Inherited variation in the androgen pathway meta-regression analysis. Lancet 2004;363:1346–1353.

98 Schelman WR, Liu G, Wilding G et al. A phase I study of zibotentan (ZD4054) in patients with metastatic castrate-resistant prostate cancer. Invest New Drugs 2011;29:118–125.

99 Sissung TM, Danesi R, Price DK et al. Association of the CYP1B1*3 allele with survival in patients with prostate cancer receiving docetaxel. J Clin Oncol 2008;26:842–847.

100 Sissung TM, Danesi R, Price DK et al. Association of the CYP1B1*3 allele with survival in patients with prostate cancer receiving docetaxel. Mol Cancer Ther 2008;7:19–26.