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Angiogenesis Inhibitors in the treatment of Prostate Cancer

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Abstract

Importance of the Field—Prostate carcinoma is the most common non-cutaneous malignancy in American men. The efficacy of docetaxel and prednisone in metastatic castrate-resistant prostate cancer (mCRPC) has been shown to improve overall survival however its effect is not durable highlighting the need for new therapies.

Areas covered in this Review—We will review the development of some of the leading compounds with direct and indirect anti-angiogenic activity in prostate cancer including antibodies to vascular endothelial growth factor and its receptors, small molecule inhibitors of downstream signaling, immunomodulatory drugs with anti-angiogenic activity, and compounds thought to directly inhibit or destroy vascular endothelial cells.

What the reader will gain—The reader will gain a basic understanding of the role of angiogenesis in prostate cancer growth and metastasis. Current and potential targets of angiogenesis and their corresponding drugs under development for prostate cancer are discussed.

Take Home Message—There are now multiple early phase clinical trials of anti-angiogenic agents alone or in combination in prostate cancer. Several of these are now in phase III development. Combined therapy with two or more anti-angiogenic compounds may improve the activity of either compound alone. Multiple targets in the angiogenesis pathway continue to be elucidated and should remain an active area of investigation for the treatment of prostate cancer.

1 Introduction

1.1 Epidemiology and Natural History

In the United States, prostate cancer is the leading non-cutaneous malignancy in men with an estimated 192,280 new diagnoses and 27,360 deaths projected for 2009. 1 Approximately 80% of cases are diagnosed with localized disease and treatment strategies for these patients include active surveillance, radiation therapy or surgery. While often effective, definitive surgery with radical retropubic prostatectomy has been shown to have biochemical recurrence rates of up to 32% at 10 years. 2 For those patients receiving curative external beam radiation therapy, a study of 1,044 patients treated between 1977 and 1991 reported a 60% 10-year biochemical recurrence rate for T1-2 patients. 3 For those who progress or present at diagnosis with advanced or metastatic disease, androgen deprivation therapy (ADT) can be effective. The Medical Research Council completed a randomized trial of 938 patients with advanced or asymptomatic metastatic prostate cancer evaluating early versus late ADT and reported an improvement in overall survival for those treated with ADT early. There were also quality of life benefits including reduction in pathologic fracture, spinal cord compression and ureteral

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obstruction. 4 Unfortunately, the median duration of response to androgen deprivation therapy is limited to approximately 14 to 20 months. 5 There are several second line hormonal therapies available, however the vast majority of patients will eventually become castration resistant. In 2004, two phase III trials demonstrated docetaxel with either prednisone or estramustine offered castration resistant prostate cancer (CRPC) patients an improvement in overall survival and quality of life over mitoxantrone based regimens. 6 7 Every 3 week docetaxel and daily prednisone was FDA approved in May of 2004 and is now considered to be either the backbone or comparator for trials of new agents to treat metastatic CRPC. 8 Median survival for CRPC patients treated with docetaxel is now approximately 18 to 20 months. After progression on docetaxel, CRPC patients have a very poor prognosis with median survival of approximately 6 to 10 months. 9 It is clear that more effective agents are needed in this population and targeting of the angiogenesis pathway is one strategy that is actively being pursued.

1.2 Rationale for targeting angiogenic pathway

The observation that intense neovascularization is seen surrounding growing tumor was described as early as 1939 by Ide and colleagues. 10 It was later discovered that angiogenesis is required to feed the continued growth of a malignant mass and that in the absence of neovascularization, tumor growth would halt at a diameter of 2–3 mm. 11 Once tumor cells are able to recruit their own blood supply, they may further expand and metastasize, a process that has been termed the “angiogenic switch” 12. The role of angiogenesis in tumor biology was studied intensely by Judah Folkman’s group in the early to mid 1970s. 13 14 Several early studies suggested that there was a humoral inducer of angiogenesis that was concentrated near malignant cells. 15 16 The subsequent isolation of basic fibroblast growth factor (bFGF) 17 and vascular permeability factor (VPF) 18 also called vascular endothelial growth factor (VEGF) ignited further scientific interest in characterizing the angiogenesis pathway. While the activation of VEGF receptors by VEGF is important, the current model of angiogenesis involves tumor cells, the extracellular matrix and endothelial cells participating in a complex interaction with pro-and anti-angiogenic factors thought to be fueled by a hypoxic microenvironment. A detailed description of the molecular mechanisms involved in the angiogenesis pathway is outside of the scope of this review and the reader is referred to the recent excellent overview by Li and colleagues. 19 The manipulation of the dynamic process of angiogenesis with novel compounds to treat multiple malignancies is an active area of investigation..

Angiogenesis appears to play a critical role in prostate cancer with several studies correlating markers of angiogenesis with metastatic disease, higher gleason grade and clinical outcomes. Weidner showed that microvessel density (MVD) was significantly higher in prostate cancer samples for those patients with metastatic disease when compared with those without metastatic disease. 20 A 1998 study by Borre of 221 prostate cancer patients followed for a median of 15 years revealed that MVD of tumor samples at diagnosis was statistically significantly correlated with stage, grade and disease specific survival. 21 Furthermore, serum levels of the humoral ligand vascular endothelial growth factor (VEGF) were found to be significantly higher in those prostate cancer patients with metastatic disease. 22 Plasma VEGF levels have also been shown to be an independent prognostic factor in men with metastatic prostate cancer. 23 24 Finally, a key mediator of VEGF expression, hypoxic-inducible factor (HIF), has higher expression in prostate cancer than in benign prostate tissue. 25 Based on these findings, angiogenesis inhibition has been targeted as a strategy to treat prostate cancer.

Both basic and clinical studies have shown that inhibition of angiogenesis can inhibit tumor progression and metastases. 26 There are several ways one can inhibit angiogenesis: inhibit proangiogenic factors such as VEGF, inhibit receptors of proangiogenic factors (VEGF-receptors), raise the concentration of antiangiogenic factors or directly kill tumor-related

vascular endothelial cells. In this review we discuss multiple agents which are actively being developed to take advantage of several of these targets. (Fig. 1)

2 Body

2.1 Targeting VEGF

Bevacizumab (Avastin; Genentech, San Francisco, CA) is a recombinant humanized anti-VEGF antibody which has been shown to have activity in multiple cancer cell lines and is currently FDA approved for treatment of several malignancies including colorectal carcinoma, non-squamous non-small cell lung cancer, metastatic breast cancer, recurrent glioblastoma and most recently metastatic renal cell carcinoma. 27 The single agent activity of bevacizumab in prostate cancer was initially reported by Reese and colleagues in 2001. In this small phase II trial, 15 patients with metastatic castrate resistant prostate cancer (mCRPC) who had not received prior chemotherapy received 10 mg/kg of bevacizumab every 14 days. While 4 patients (27%) had PSA declines of <50%, there were no objective responses (defined by RECIST criteria or PSA declines $\geq$ 50%) and the trial was halted prior to planned second and third stages of enrollment based on not meeting predefined response goals. 28 Despite the disappointing single agent data, several trials have demonstrated activity when bevacizumab is combined with chemotherapy. CALGB 90006 was a phase II trial of docetaxel at 70 mg/m² and bevacizumab 15 mg/kg given on day 2 every three weeks with estramustine 280 mg three times daily on days 1 through 5. Decadron was given 8 mg twice daily on days 1 through 3 and warfarin given at 2 mg daily was encouraged. 29 On the most recent follow up, 79 patients with CRPC (median Gleason score of 8) had been enrolled with 42% (14/33) of those with measurable disease achieving a partial response and 79% obtaining a >50% PSA decline. 30 More recently, DiLorenzo published a small phase II trial of bevacizumab and docetaxel in 20 docetaxel-pretreated mCRPC patients demonstrating a 37.5% overall response and median overall survival of 9 months. 31 A phase III randomized trial of every three week docetaxel (75 mg/m²) with 10 mg daily prednisone with or without 15 mg/kg bevacizumab was commenced and closed to accrual in 12/2007 (CALGB 90401). 32

Dual anti-angiogenic therapy with bevacizumab and thalidomide has also been evaluated. Thalidomide is an oral compound with immunomodulatory and anti-angiogenic effects that will be discussed later in this review. Based on data suggesting that thalidomide decreases multiple markers of angiogenesis but does not reliably decrease VEGF levels³³, the National Cancer Institute developed a protocol adding thalidomide and bevacizumab to standard of care docetaxel. In this trial, 60 patients with chemotherapy naïve metastatic CRPC received bevacizumab 15 mg/kg day 1, docetaxel 75 mg/m² day 1, thalidomide 200 mg by mouth once daily and prednisone 5 mg twice daily (ATTP) all given on an every 3 week cycle with venous thromboembolic (VTE) prophylaxis. Impressive preliminary results of the ATTP regimen were reported in 2008 and revealed a PSA decline of >50% in 88% (51/60) with durable PSA decline extending to a median of 11 cycles. Of the 32 patients with measurable disease, two patients had complete responses and 18 had a partial response for an overall response rate of 62.5%. Median progression free survival was 18.2 months and median overall survival 26.7 months. 34 The regimen was reasonably well tolerated with a median on-study duration of 12 cycles. A peer-reviewed manuscript documenting the trial and its most current updated results has been recently accepted for publication.

Bevacizumab has also been combined with immunotherapy and other experimental agents. In a phase II study, prostatic acid phosphatase-pulsed dendritic cells (APC8015; Provenge, Dendreon Pharmaceuticals, Seattle, WA) were combined with bevacizumab for biochemical recurrence after definitive local therapy. The combination was found to induce an immune response and slow serum PSA doubling time. 35 The combination of Satraplatin, a third generation oral platinum compound (Spectrum Pharmaceuticals, Irvine, CA), and bevacizumab

is being studied in CRPC patients who have previously been treated with docetaxel (NCT00499694). Bevacizumab is actively being studied in several other combinations in early and late stage prostate cancer (see table 1).

Another promising agent Aflibercept (AVE0005) (Sanofi-Aventis/Regeneron) is a novel fusion protein of domain 2 of VEGFR-1 and domain 3 of VEGFR-2 with the Fc fragment of IgG1. This compound, also known as VEGF-Trap, acts as a soluble decoy VEGF receptor that can sequester VEGF.³⁶ Multiple phase II studies have been reported in patients with ovarian, non-small cell lung and other solid tumors revealing anti-tumor activity and reasonable side effect profile.^{37, 38} Based on these preliminary findings and the role of angiogenesis in prostate cancer, a large multicenter, randomized, double blind placebo controlled trial is being conducted to compare the efficacy and safety of aflibercept versus placebo with docetaxel and prednisone for metastatic CRPC. (Table 1)

2.2 Targeting VEGF-receptors

2.2.1 Extracellular VEGFR agents—Compounds targeting the extracellular domain of the VEGF receptor are under study but are still relatively early in development. Ton and colleagues published phase I results of CDP791, a di-Fab' polyethylene glycol (PEG) conjugate that inhibits VEGFR-2 in vitro and angiogenesis in vivo. 12 patients were treated in the phase I setting and the drug was felt to be biologically active and well tolerated.³⁹ Camidge presented preliminary data from a Phase I study of IMC-1121(B) a monoclonal antibody to VEGFR-2.⁴⁰ A large randomized phase II trial of IMC-1121 in addition to mitoxantrone and prednisone in CRPC following progression on docetaxel is underway.(NCT00683475) Another antibody to the extracellular binding domain of VEGFR-1, IMC-18F1, is also being studied in the phase I setting.⁴¹

2.2.2 Intracellular selective VEGFR antagonists—AZD-2171 (Cediranib®, Astra Zeneca, Wilmington, DE) is an indole-ether quinazoline with potent and selective ATP-competitive inhibition of VEGF-receptors 1 and 2.⁴² This oral tyrosine kinase inhibitor (TKI) is actively being developed in multiple malignancies including prostate cancer. In the CRPC setting, a phase I study looked at 26 patients and established a MTD dose of 20 mg with grade 3 toxicity of muscle weakness and fatigue.⁴³ There was one objective response and several PSA declines that occurred *after* discontinuation of therapy based on PSA progression, challenging the use of PSA as a marker of antitumor effect for this compound. A phase II trial of Cediranib in metastatic CRPC with progression following docetaxel is ongoing at the National Cancer Institute (NCT00436956). Cediranib is given at a dose of 20 mg by mouth daily and in a second cohort given with concurrent daily oral prednisone on 28 day cycles. Progression is defined by clinical or radiographic evidence rather than PSA rise alone. Updated results of the first 34 patients were presented by Karakunnel in 2009.⁴⁴ Thirteen of the twenty-three patients with measurable disease had some tumor shrinkage with 4 meeting the criteria for partial response. PSA levels have not correlated well with response, further supporting the idea that PSA may be an unreliable marker for disease surveillance when using this compound. The main toxicities were hypertension, dysphonia and fatigue. DCE-MRI, which has been studied as a pharmacodynamic imaging strategy for cediranib⁴⁵, was performed on all patients and results of the clinical correlation of DCE-MRI will be forthcoming.

2.2.3 Intracellular non-selective inhibitors of the VEGFR—There are now multiple agents with activity that includes, but is not limited to, the intracellular domain of the VEGF family of receptors. These compounds, largely tyrosine kinase inhibitors (TKIs), are being actively studied in multiple different malignancies and are in various stages of development. (Table 2) One such agent that has been studied in prostate cancer is sorafenib (Nexavar®, Bayer HealthCare and Onyx Pharmaceuticals, Emeryville, CA). This agent is a small molecule

tyrosine kinase inhibitor (TKI) which targets RAF kinase in addition to VEGFR-2 and PDGFR-beta resulting in anti-proliferative and anti-angiogenic effects. ⁴⁶ The agent is currently FDA approved for hepatocellular carcinoma and renal cell carcinoma. Several phase II trials of sorafenib in prostate carcinoma have been conducted. Our group conducted a single arm open label trial of single agent sorafenib given at 400 mg by mouth twice daily continuously on 28 day cycles. Initial results from the first 22 CRPC patients enrolled showed no PSA declines >50%. There was discordance between PSA and radiographic response criteria with 2 patients progressing by PSA criteria but having a decrease in the number of lesions seen on bone scan. Of the 21 patients with progressive disease, 13 were based on PSA only and had otherwise stable clinical and radiographic disease. ⁴⁷ The second stage of the study enrolled 24 additional patients with progression redefined as clinical or radiographic criteria alone. 21 of the 24 patients had previous docetaxel therapy and the median Gleason score was 8. One patient had partial response and 10 patients had stable disease. Median progression free survival was 3.7 months and median overall survival was 18.0 months. Pooled data from both stages of the trial (N=46) revealed a median survival of 18.3 months. ⁴⁸ Another phase II trial in chemotherapy naïve metastatic or CRPC patients enrolled 57 patients who were to receive 400 mg twice daily sorafenib. Of the 55 evaluable patients, only 2 had PSA decline >50% and none had objective responses by RECIST. Nonetheless, 15 had stable disease and 31% of patients had not progressed by 12 weeks. ⁴⁹ Chi et al reported their phase II findings in 2008 with 28 chemotherapy naïve patients with CRPC. ⁵⁰ The number of patients with PSA decline >50% was only 3.6%, however PSA declines were seen post-discontinuation of therapy, again suggesting that the agent may lead to increased serum PSA levels independent of tumor growth. Since these trials have been completed there has been discussion regarding PSA as an endpoint in phase II trials of CRPC ⁵¹ and the Prostate Cancer Clinical Trials Working Group does not recommend removing patients from study based on rising PSA alone. ⁵² A review of the safety profile and adverse events from studies involving sorafenib combined with chemotherapies or other targeted agents was recently published. ⁵³ Encouraging preliminary results from a phase I trial of sorafenib in combination with docetaxel and prednisone were presented by Mardjuadi demonstrating 15 of 20 patients with PSA decline >50% although a significant number of febrile neutropenia was noted. ⁵⁴ Based on the preliminary studies of sorafenib in prostate cancer, the agent continues to be actively pursued alone and in combination with other therapies. (Table 3)

There are many other nonselective TKIs being developed for multiple malignancies including prostate cancer. SU5416 (Semaxinib[®], Pharmacia, San Francisco, CA) is a synthetic TKI that reversibly inhibits VEGFR-2 and KIT. ^{55, 56} A phase II study of 36 patients with CRPC receiving SU5416 + dexamethasone pretreatment versus dexamethasone alone revealed no significant meaningful clinical activity. ⁵⁷ This, in addition to inconvenient IV dosing requiring a central line, and modest toxicity led to the decision to halt further development of this agent in prostate cancer.

SU11248/Sunitinib (Sutent[®], Pfizer Inc. New York, NY) is an oral multi-tyrosine kinase inhibitor with activity against VEGFR-2, PDGFRb, FLT-3 and KIT. ⁵⁸ Sunitinib (SU) is currently FDA approved for gastrointestinal stromal tumor (GIST) after failure of imatinib and advanced/metastatic renal cell carcinoma. A phase I trial of SU in addition to docetaxel and prednisone in CRPC showed the regimen to be safe and tolerable with 1/7 evaluable patients having partial response and four additional with stable disease. ⁵⁹ Updated results from the phase I/II trial of SU combined with docetaxel and prednisone were recently presented. ⁶⁰ Patients received SU at 37.5 mg/d on days 1–14, docetaxel 75 mg/m² on day 1 and prednisone 5 mg twice daily days 1–21 on 21 day cycles and the primary endpoint was PSA decline by PSA working group criteria. 55 patients were enrolled and 36 discontinued therapy (16 for disease progression and 13 for adverse events). Most common grade 3–4 AEs were neutropenia (75%), febrile neutropenia (15%) and fatigue (15%). Sunitinib dose reductions were required

in 26% of patients and docetaxel dose reduction necessary in 33%. Thirty nine percent of evaluable patients had a partial response. PSA declines occurred in 56% and median TTP was 42 weeks. Median progression free and overall survival had not yet been reached. Another ongoing phase II study is evaluating neoadjuvant androgen deprivation therapy with concurrent daily SU at 37.5 mg daily given for 90 days prior to definitive surgery for high risk local prostate cancer. Early results were presented and showed one pathologic CR out of 30 was obtained. 61 Sunitinib is actively being studied with and without docetaxel in several other clinical trials. There is also a large phase III international trial comparing Sunitinib and prednisone with prednisone alone in CRPC patients who have failed docetaxel based therapy. (Table 3)

Vandetanib (ZD 6474, Zactima™, Astra Zeneca) is a once daily oral multi-tyrosine kinase inhibitor targeting the VEGFR, EGFR and RET pathways. 62 Vandetanib has shown promise in non-small cell lung cancer (NSCLC) with results from a randomized phase II trial revealing an improvement in progression free survival at 300 mg once daily when compared to gefitinib. 63 These results have led to several large phase III trials of vandetanib with and without docetaxel in NSCLC. Vandetanib is currently being investigated in several phase II trials for prostate cancer in both the metastatic and non-metastatic castrate resistant setting. (Table 3) Another non-selective TKI in early development for prostate cancer is GW786034 (Pazopanib®, GlaxoSmithKline, London, United Kingdom). This agent is an oral multi-targeted TKI that targets VEGF, PDGFR and KIT. Pazopanib has a robust amount of early phase data in other malignancies and is currently in phase III clinical trials for ovarian cancer, soft tissue sarcoma, inflammatory breast cancer and renal cell carcinoma. Several phase II clinical trials are actively recruiting patients in the chemotherapy naïve prostate cancer setting. (Table 3)

Downstream VEGF receptor targets have also been evaluated in prostate cancer. Ly317615 (Enzastaurin, Ely Lilly, Indianapolis, IN, USA) is a potent and selective serine/threonine kinase inhibitor that targets protein kinase C (PKC), a downstream kinase involved in VEGFR signal transduction. Preclinical studies reveal enzastaurin can lead to inhibition of new vessel growth in the rat corneal micropocket assay 64 as well as decrease MVD and VEGF levels in human tumor xenografts. 65 66 A randomized double blind placebo controlled phase II trial of docetaxel and prednisone with and without enzastaurin for front line treatment of CRPC is actively recruiting patients. (NCT00466440)

2.3 Targeting the tumor vascular endothelium

2.3.1 Metronomic Chemotherapy (MC)—In 1991, Kerbel proposed the idea that targeting the more genetically stable tumor vascular endothelial cell may bypass the typical acquired drug resistance that has plagued traditional cytotoxic chemotherapy. 67 The more rapid cycling of immature tumor endothelial cells may also offer the specificity required to obtain a therapeutic index and avoid unwanted toxicity to normal vasculature. In 2000, Hanahan coined the term “metronomic” chemotherapy (MC) to describe the frequent administration of chemotherapy at doses well below the MTD with no prolonged drug free breaks. 68 Preclinical data has suggested that MC can overcome drug resistance. 69 This effect of overcoming resistance by using more frequent dosing has clinical precedent with etoposide in lung cancer 70 and paclitaxel in breast cancer. 71 Further preclinical studies have demonstrated the anti-angiogenic and antitumor effects of MC delivered with multiple agents including taxanes, cyclophosphamide, vinblastine, etoposide and platinum. 72 The metronomic strategy is thought to provide direct endothelial cytotoxicity as well as upregulate endogenous endothelial cell inhibitors like thrombospondin-1 73. Studies have also supported an immune-stimulatory effect with reduction of T-regulatory cells. 74

Initial evidence of the utility of MC in prostate cancer came from Gode and Colleagues in 2003. This was a retrospective case series of 34 CRPC patients treated with metronomic

cyclophosphamide (mCTX) (50 mg daily) and dexamethasone (1 mg daily). Patients had a mean on-study PSA of 154 and over half had bone or soft tissue disease with 13 patients having received prior chemotherapy. Only 1 patient was taken off therapy secondary to treatment related toxicity and 69% of patients had a PSA decline >50%.⁷⁵ Following these results, a single center prospective open label phase II trial of mCTX alone enrolled 80 patients with CRPC. 76 Patients received 50 mg/d of oral CTX and were evaluated for PSA decline and objective tumor response by RECIST. 58 patients completed two cycles (8 weeks) and were included in the intent to treat analysis. Forty five percent of patients had a WHO performance status 2. Response by traditional criteria was marginal with 5.2% (3/58) having either PSA reduction >50% or objective tumor response. An additional 39% of patients had some decline in PSA or improved PSA velocity and the median overall survival had not yet been reached. The most concerning toxicity was grade 3 lymphopenia in 32.8%, none of whom had opportunistic infections. The study was limited by short follow up and 22 patients who were not included in the intention to treat analysis, 15 of whom had rapidly progressive PSA or progressive symptoms. Recently, a prospective non-randomized phase II study published by Fontana treated 28 advanced metastatic CRPC (68% docetaxel resistant) patients with mCTX (50 mg PO daily), dexamethasone (1 mg daily) and celecoxib (200 mg twice daily) after receiving one upfront IV dose of CTX at 500 mg/m². Thirty two percent (9/28) of patients had PSA decline >50% and median overall survival was 21 months.⁷⁷

The benefits of metronomic chemotherapy include low toxicity and low cost as well as ease of administration. Early preclinical studies suggested a benefit from combining targeted anti-angiogenesis compounds such as TNP-470 with MC.⁶⁹ A phase I study has been published by Di Lorenzo who used mCTX (50 mg/d) with concurrent thalidomide in CRPC patients who had failed docetaxel chemotherapy. MTD was 100 mg daily thalidomide and the most common adverse effects were fatigue, constipation and peripheral neuropathy. Two evaluable patients had >50% PSA decline (15%) and one other had PSA decrease <50%.⁷⁸ Further studies combining MC with targeted anti-angiogenic therapies are underway in hopes of increasing anti-tumor effects.

2.3.2: Prostate Specific Membrane Antigen (PSMA)—Prostate specific membrane antigen (PSMA) is a type 2 integral transmembrane glycoprotein expressed preferentially on prostate epithelial cells. Although its role in malignancy is unclear, it is currently an active candidate for research into both the diagnosis and treatment of prostate cancer. 19 PSMA is preferentially and highly expressed in advanced prostate cancer versus benign prostatic tissue.⁷⁹ Because PSMA has been shown to be expressed on the neovasculature of multiple tumors but not on normal vasculature⁸⁰, it has been identified as a target for anti-angiogenic therapy. Several PSMA antibodies have been developed⁸¹, the most studied has been human recombinant monoclonal antibody J591 (MLN J591, BZL Biologics, Millenium, Cambridge, MA). Initial phase I studies of the antibody showed excellent targeting and a phase II trial of the naked antibody given with interleukin 2 demonstrated acceptable tolerability but no PSA declines >50%.⁸² Results with J591 radio-labeled with 177-lutetium⁸³ and 90-Yttrium⁸⁴ have revealed specific targeting of prostate cancer metastases with acceptable toxicity and more appreciable biologic activity. A trial of 177-Lu-J591 with Docetaxel and Prednisone in CRPC is actively recruiting patients (Table 3).

2.4 Antiangiogenic/Immunomodulatory Agents: Thalidomide and Lenalidomide

Thalidomide (Thalomid®, Celgene Corporation, Summit NJ) is an oral agent with anti-tumor efficacy demonstrated in several malignancies and is currently FDA approved for newly diagnosed Multiple Myeloma. While its mechanism is not clearly elucidated, Thalidomide and its analogs appear to inhibit angiogenesis in part by affecting the platelet derived growth factor receptor pathway.⁸⁵ Furthermore, preclinical data has demonstrated that thalidomide may

increase the number of apoptotic circulating endothelial cells.⁸⁶ Aside from its possible anti-angiogenic activity, thalidomide and its derivatives lenalidomide and pomalidomide may have immunomodulatory effects including T-cell co-stimulation, T-regulatory cell inhibition (lenalidomide and pomalidomide) and enhanced NK cell activity.^{87, 88} The agent was initially used as a sedative/anti-emetic until it was discovered to be teratogenic and was taken off the market in the 1960s.^{89, 90} In 1994 D'Amato revealed that thalidomide inhibits angiogenesis in a rabbit cornea micropocket assay⁹¹, prompting further study of this agent as a anti-angiogenic compound to combat malignancy.

An early phase II open label trial of 100 mg daily of thalidomide in CRPC patients reported by Drake and colleagues resulted in >50% PSA reduction in 15% (3/20) of patients.⁹² Another open label randomized phase II trial at the National Cancer Institute compared thalidomide at 200 mg per day with higher doses up to 1200 mg daily in 63 patients (50 low dose and 13 high dose). Eighteen percent of patients had a PSA decline of >50% and 27% had declines of >40%.³³ The authors noted that preclinical studies had shown that thalidomide may increase PSA secretion⁹³ and thus the activity was thought to warrant further study. Additionally, there were decreases in PET uptake on experimental PET scans performed during the trial, suggesting anti-tumor activity.^{94, 95}

Thalidomide has also been used in combination with cytotoxic agents. A phase 2 randomized study of weekly docetaxel (30 mg IV per week for 3 weeks on 28 day cycles) with or without 200 mg of daily thalidomide was completed in chemotherapy-naïve metastatic CRPC.⁹⁶ At a median 26 month follow up, 75 patients had been enrolled (25 docetaxel alone and 50 docetaxel + thalidomide). While not reaching statistical significance, the endpoints of >50% PSA reduction (53% vs. 37%) and median PFS (5.9 mo vs. 3.7 mo) favored the combined arm.⁹⁷ In an updated analysis with median follow-up of 46.7 months, median overall survival met statistical significance with a median OS of 25.9 months for the combined arm versus 14.7 months for docetaxel alone $P=0.0407$.⁹⁸ However, 12 of the first 43 patients in the combined group suffered thromboembolic events. As such, prophylactic anticoagulation with low-molecular weight heparin was offered to patients for the remainder of the study. Other important toxicities included a higher number of patients with fatigue, depression, neuropathy and pleural effusions in the combined arm. Several other studies have shown excellent antitumor activity combining thalidomide with estramustine and taxanes,^{99, 100} however excess toxicity has been a problem with estramustine based regimens. Thalidomide has also been looked at in patients earlier in the course of prostate cancer with PSA recurrence following definitive local therapy in several phase II trials with encouraging results.^{101, 102}

Because of the excess thrombotic events, fatigue and neuropathy associated with thalidomide, there is interest in developing other potent thalidomide derivatives such as lenalidomide in hopes of building on thalidomides activity while improving its toxicity profile. Lenalidomide (Revlamid®, Celgene Corporation, Summit, NJ) is a thalidomide analog currently FDA approved for multiple myeloma and low risk 5q-myelodysplastic syndrome. In a phase I trial of lenalidomide alone in patients with refractory solid tumors, doses as high as 35 mg per day for 21 days with a 7 day rest period were tolerated (a dose well above the dose for multiple myeloma or MDS). Stable disease was documented in 12 of 44 evaluable patients, 9 of whom had prostate cancer.^{103, 104} Another phase I study looked at lenalidomide in addition to docetaxel. 33 patients with advanced solid tumors received lenalidomide on day 1–14 and docetaxel on day 1 in 21 day cycles.¹⁰⁵ Pegfilgrastim was added on day 2 secondary to myelosuppression. The trial reached an MTD of 75 mg/m² of docetaxel with 25 mg of lenalidomide given daily on days 1–14 and further follow up demonstrated a 3% response rate with 69% stable disease.¹⁰⁶ Moss and colleagues administered lenalidomide combined with every 3 week docetaxel and prednisone in a phase I trial of 19 CRPC patients. This trial revealed a 38.5% partial response (5/13) in those with measurable disease. An additional 7 of the 13

patients had stable disease and 47% (9/19) of the patients had a PSA decline >50%.¹⁰⁷ A phase I study of weekly paclitaxel and lenalidomide 21 out of 28 days in metastatic CRPC with prior taxane treatment had minimal activity with high levels of dose limiting toxicities.¹⁰⁸

Lenalidomide has been added to ketoconazole in the chemotherapy-naïve CRPC setting. Preliminary phase II results of 18 evaluable patients were reported in 2008. After a median of 2 cycles, 10 of 18 patients had a PSA decline >50% and 3 of 4 patients with soft tissue disease had a partial response.¹⁰⁹ Building on the results of the ATTP trial with dual anti-angiogenesis agents thalidomide and bevacizumab, a phase II trial of ART-P (Avastin, Revlamid, Taxotere and Prednisone) is currently underway. (Table 1) Other thalidomide analogs including CPS 11 and CPS 49 have shown some preclinical activity.¹¹⁰

2.5 Hypoxia and Angiogenesis

Hypoxia in the tumor microenvironment plays a significant role in prostate cancer by stimulating angiogenesis as well as protecting prostate tumor cells from androgen deprivation therapy, chemotherapy and radiation cytotoxicity. Hypoxia-inducible factor 1 (HIF-1) alpha is a transcriptional regulator that responds to hypoxic conditions and has been implicated in angiogenesis in part by activating VEGF and VEGF receptor transcription.¹¹¹ HIF-1 alpha is overexpressed in prostate cancer¹¹³ and is considered a potential therapeutic target. Preclinical data on RX-0447, an anti-sense HIF-1 alpha inhibitor, has demonstrated inhibition of growth in PC-3 prostate cancer cell lines as well as prostate xenografts¹¹⁴. Further development of HIF-1 alpha targeted compounds in prostate cancer may be promising. Cyclooxygenase 2 (COX-2) is an inducible enzyme which is upregulated in prostate cancer and involved in hypoxia-induced VEGF expression via upregulation of HIF-1 alpha.¹¹⁵ While other mechanisms for COX-2 inhibition's role in anti-tumor activity have been proposed, including BCL-2 downregulation and possible AKT pathway inhibition, a recently published pilot study of 45 prostate cancer patients randomized to celecoxib or placebo prior to prostatectomy revealed a trend toward decreased markers of angiogenesis including HIF-1 and VEGF as well as decreased proliferation (MIB-1) on their prostatectomy specimens.¹¹⁶ The use of celecoxib in addition to metronomic cyclophosphamide and dexamethasone in mCRPC has been discussed in the metronomic chemotherapy section.⁷⁷ Another phase II trial looked at celecoxib at 400 mg twice daily given to 40 patients with biochemical recurrence (no evidence of metastasis) following radical prostatectomy or radiation. In this study, 90% of patients had slowing of their rate of PSA increase after 3 months of treatment indicating a potential use for celecoxib in delaying time to androgen deprivation therapy in this population.¹¹⁷ The potential anti-tumor effect of COX-2 inhibitors must be weighed against the increased cardiac risk of the use of these medications.¹¹⁸

3 Expert Opinion

There is now ample early phase clinical data to support the continued investigation of angiogenesis inhibitors in prostate cancer. (Table 4) While initial results of single agent trials of anti-angiogenic (AA) therapies alone have suggested only modest benefit, combining 2 AA agents (Bevacizumab and Thalidomide) or combining AA agents with chemotherapy appears to have a more robust anti-tumor effect. Our experience with dual-anti-angiogenic therapy in the ATTP trial³⁴ supports further research into this strategy and we eagerly await accrual and results from the ART-P trial using lenalidomide in place of thalidomide with the hope that anti-tumor efficacy is maintained with an improved adverse event profile. The phase III trial of docetaxel and prednisone with or without bevacizumab will also be instructive and may change the standard of care for metastatic or clinically progressive CRPC. Further study of newer agents targeting the angiogenic pathway both alone and in combination are underway. Early stage trial design for targeted therapies must take into account the lack of reliability of PSA as a surrogate marker. While PSA decline has been used in evaluation of cytotoxic agents with

some success, there are now several examples of the limitations of this endpoint in trials of small molecules and immunotherapy. In two phase II studies of sorafenib, PSA declines were seen after discontinuation of therapy and bone disease was seen to improve in the face of rising PSA.⁴⁷⁻⁵⁰ There are also examples of vaccine trials where progression free survival endpoints were not met despite overall survival being statistically in favor of the experimental arm.^{119, 120} We strongly encourage investigators to follow the recommendations of the PSA working group and discourage taking patients off trial for PSA progression alone. Further development of markers of anti-tumor activity including circulating tumor cell analysis and dynamic imaging should also be explored. Finally, the idea of exerting a constant pressure on prostate cancer may be a promising strategy. To this end, metronomic chemotherapy (MC) may be a cost-effective and well tolerated option as one part of a multi-agent regimen. While clinical trials of anti-angiogenic compounds have shown some promise in prostate cancer, mCRPC continues to be incurable with the goal being improvement in the quality and quantity of life for these patients. To this end, continued investigation into multiple combination therapies involving single or dual agent AA agents with or without cytotoxic chemotherapy, MC or immunotherapy should continue to be explored.

Article Highlights Box

- Angiogenesis plays an important role in prostate cancer growth and metastasis.
- Increased levels of VEGF correlate with metastasis and survival in prostate cancer.
- CALGB 90401, a large phase III trial of Docetaxel and Prednisone with or without Bevacizumab, has completed enrollment. Forthcoming results may lead to a change in the standard of care for treatment of metastatic castrate resistant prostate cancer.
- Phase 2 data on thalidomide and bevacizumab in addition to standard chemotherapy supports the potential role for dual anti-angiogenic therapy in castrate resistant prostate cancer.
- Treatment of mCRPC with agents targeting the angiogenesis pathway continues to be an area of active investigation.

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Figure 1.

A simplified diagram of the angiogenesis pathway with anti-angiogenic targets and select compounds exploiting them. Legend: VEGF: vascular endothelial growth factor, bFGF: fibroblast growth factor, PDGF: platelet derived growth factor, AT-III: antithrombin III, PSMA: prostate specific membrane antigen.

Table 1

Select active clinical trials of VEGF-directed compounds bevacizumab and aflibercept in prostate cancer

Phase	Regimen	Goal N	Clinical Trials ID
Bevacizumab			
I	Dasatinib and Bevacizumab in Treating Patients With Solid Tumors That Are Metastatic or Cannot be Removed by Surgery	48	NCT00792545
II	Bevacizumab, Lenalidomide, Docetaxel, and Prednisone (ART-P) for Treatment of Metastatic Castrate-Resistant Prostate Cancer	57	NCT00942578
II	Bevacizumab in Combination With Hormonal and Radiotherapy in Patients With High-Risk Prostate Cancer	18	NCT00349557
II	Satraplatin and Bevacizumab in CRPC patients previously treated with docetaxel	24	NCT00499694
II	Androgen Deprivation Therapy +/- Bevacizumab for PSA Recurrence of Prostate Cancer After Definitive Local Therapy	100	NCT00776594
II	Avastin, Docetaxel and Androgen Deprivation Followed by Continued Avastin and Androgen Deprivation for Men With a Rising PSA After Local Therapy	42	NCT00658697
III	Docetaxel and prednisone with or without bevacizumab for mCRPC (enrollment complete)	1020	NCT00110214
Aflibercept			
III	Docetaxel and prednisone with or without Aflibercept in mCRPC	1200	NCT00519285

Table 2

Tyrosine kinase inhibitors (TKI) with VEGF receptor activity. Based on Table 1 from Chu, Expert Opin. Biol. Ther. (2009) 9(2): 263–271. By permission of Quincy Chu).

Drug	Mechanism of Action	Company	Current Stage of Development
<i>Predominant class III tyrosine kinase inhibitors</i>			
ABT-869	VEGFR-2/PDGFR beta	Abbott	II
Axitinib	VEGFR-1, 2, 3/C-KIT/PDGFR beta	Pfizer	II/III
AMG 706	VEGFR-1, 2, 3/PDGFR alpha/C-KIT/RET	Amgen	II/III
BAY 57-9352	VEGFR-2, 3/PDGFR/C-KIT	Bayer	I
Brivanib	VEGFR-1, 2/FGFR-1	Bristol Meyer Squibb	II/III
BIBF 1120	VEGFR-1,2,3/FGFR-3/PDGFR alpha	Boehringer-Ingelheim	II/III
Cediranib	VEGFR-1,2,3/PDGFR alpha/C-KIT	AstraZeneca	II/III
Pazopanib	VEGFR-1,2,3/PDGFR alpha/C-KIT	GlaxoSmithKline	II/III
Sorafenib	VEGFR-2,3/PDGFR alpha/FLT-3/C-KIT	Bayer	III and FDA approved for renal cell carcinoma and HCC
Sunitinib	VEGFR-1,2/C-KIT/FLT-3/PDGFR alpha	Pfizer	III and FDA approved for GIST and renal cell carcinoma
Vatalanib	VEGFR-1,2,3/PDGFR alpha/C-KIT/C-FOS	Novartis	III
<i>Epidermal growth factor receptor (EGFR) and VEGFR inhibitors</i>			
AEE788	EGFR/HER-2/VEGFR-2	Novartis	II
BMS-690514	Pan-HER and VEGFR	Bristol Meyer Squibb	I/II
Vandetanib	EGFR/VEGFR-2	AstraZeneca	III
XL-647	EGFR/VEGFR-2	Exelixis	I
<i>Miscellaneous multi-kinase inhibitors with VEGFR activity</i>			
CYC116	Aurora kinase/VEGFR-2	Cyclacel	I
MGCD265	VEGFR/C-MET	MethylGene	I
OSI930	VEGFR-2/C-KIT/LCK/C-RAF	OSI	I

Table 3

Select clinical trials of tyrosine kinase inhibitors and other anti-angiogenic compounds in prostate cancer.

Phase	Regimen	Goal N	Clinical Trials ID
AZD-2171 (Cediranib)			
II	AZD-2171 and prednisone in metastatic CRPC	37	NCT00436956
II	Docetaxel and prednisone with or without cediranib	104	NCT00527124
Sorafenib			
I/II	Concurrent sorafenib, ADT and radiation therapy for initial treatment of intermediate and high risk localized prostate cancer	50	NCT00924807
II	Sorafenib and docetaxel for mCRPC	69	NCT00589420
Sunitinib			
II	Sunitinib with docetaxel and prednisone in chemotherapy naïve metastatic CRPC	30	NCT00879619
II	Docetaxel, sunitinib and prednisone followed by EBRT for men with biochemical recurrence following radical prostatectomy	38	NCT00734851
II	Neoadjuvant sunitinib and hormonal ablation for patients who will have prostatectomy	42	NCT00329043
III	Prednisone with or without sunitinib in CRPC patients who have failed docetaxel	819	NCT00676650
Pazopanib			
II	Pazopanib after failure of total androgen blockade	34	NCT00945477
II	Pazopanib with or without bicalutamide in mCRPC	74	NCT00486642
Vandetanib			
II	ZD 6474 (Vandetanib) with Bicalutamide versus Bicalutamide alone in chemotherapy naïve CRPC	74	NCT00757692
II	Randomized placebo controlled trial of vandetanib and bicalutamide versus bicalutamide alone in metastatic CRPC	90	NCT00659438
Other anti-angiogenic agents			
I	Docetaxel/Prednisone and 177 Lu-J591 antibody for mCRPC	30	NCT00916123
II	177Lu-J591 and ketoconazole/hydrocortisone in high risk nonmetastatic CRPC	140	NCT00859781

Table 4

Selected studies of anti-angiogenic compounds in the treatment of prostate cancer.

Agent (Author, Year)	Phase-Population	N=	Results	Grade 3 or 4 toxicity
Bevacizumab (Reese, 2001)	II mCRPC	15	OR: 0% (0/15) PSA: 0% (0/15)	2 hyperglycemia, 1 anemia, 3 hyperkalemia (all thought to be unrelated)
Bevacizumab + Docetaxel + Estramustine (Picus, 2004)	II mCRPC	79	OR: 42% (14/33) PSA: 79%	5 VTE with 1 death mesenteric vein thrombus, 1 perforated sigmoid diverticulum, <3% febrile neutropenia
Bevacizumab + Docetaxel (DiLorenzo, 2008)	II Doc-resistant mCRPC	20	OR: 37.5% (3/8) PSA: 55% (11/20) mPFS=4 mo, mOS=9 mo	Grade 4: 1 neutropenia and 1 thrombocytopenia. Grade 3: 3 neutropenia, 2 nausea/vomiting, 1 neuropathy
Bevacizumab + Docetaxel + Thalidomide + Prednisone (Ning, 2008)	II Chemo-naïve mCRPC	60	OR: 62% (20/32) PSA: 88% (51/60) mPFS=18.2 mo, mOS=26.7 mo	febrile neutropenia (5/60), syncope (5/60), GI perforation or fistula (3/60), thrombosis (3/60), grade 3 bleeding (2/60)
AZD-2171 (Cediranib) (Karakunnel, 2009)	II Doc-resistant mCRPC	34	OR: 17% (4/23) PSA not reported mPFS and mOS not reported	vomiting (2), prolonged QTc interval (1) and muscle weakness (3), weight loss (3), dehydration (4), fatigue (6), hypoxia (1), renal failure (1), transaminitis (3), and anorexia (1)
Sorafenib (Aragon-Ching, 2009)	II 88% Doc-resistant mCRPC	24	OR: 8% (1/13) PSA not reported mPFS =3.7 mo, mOS=18 mo	Lab abnormalities (9), Dermatologic (4), Fatigue (2), Nausea (1), Anemia (1), Cath DVT (1), Infxn (1)
Sorafenib (Steinbild, 2007)	II Chemo-naïve CRPC and mCRPC	55	OR: 0% (0/55), PSA: 3.6% (2/55) mPFS= 2 mo (8 weeks) mOS= had not been reached	Dermatologic (5), Hypertension (3), Fatigue (2), Constipation (2)
Sorafenib + Docetaxel + Prednisone (Mardjuadi, 2009)	I Chemo-naïve CRPC	24	OR: not reported PSA: 75% (15/20) PFS and OS not reported	febrile neutropenia (8), uncomplicated neutropenia (5), and hand-foot syndrome (4)
Sunitinib + Docetaxel + Prednisone (Zurita, 2009)	I/II Chemo-naïve mCRPC	55	OR: 39% (13/33) PSA: 56% (31/55)	neutropenia (75%), febrile neutropenia (15%), fatigue (15%), stomatitis (7%), and anorexia

Agent (Author, Year)	Phase-Population	N=	Results	Grade 3 or 4 toxicity
			mPFS 42 weeks	(7%). 33% patients required docetaxel dose reduction.
Metronomic Cyclophosphamide (mCTX) (Lord, 2007)	II Chemo-naïve CRPC and mCRPC	58	OR: 1.7% (1/58) PSA: 3.4% (2/58) mOS had not yet been reached	Grade 3 lymphopenia in 33%. Required dose reduction in 5 patients.
mCTX + Celecoxib + Dexamethasone (Fontana, 2009)	II 68% Doc-resistant mCRPC	28	OR: 20% (1/5) PSA: 32% (9/28) mPFS=3 mo, mOS=21 mo	No grade 3 or 4 adverse events were reported.
Thalidomide (Figg, 2001)	II 74% chemo naïve CRPC and mCRPC	63	OR: 0% (0/35) PSA: 14% (9/63) mTTF: 2.1–2.2 mo mOS 15.8 mo	18 events ≥grade 3. Suicide within 30 days of study drug discontinuation in one patient. One patient developed acute AML (hx of prolonged prior cytotoxic exposure).
Thalidomide + Docetaxel (Dahut, 2004)	II Chemo naïve mCRPC	47	OR: 35% (7/20) PSA: 53% (25/47) mPFS: 5.9 mo, mOS: 25.9 mo	All grade 3: neutropenia (4), anemia (2), Thromboembolism (9), fatigue (2), Hyperglycemia (7)
Lenalidomide + Docetaxel + Prednisone (Moss, 2007)	I mCRPC w/<2 prior Chemo regimens	19	OR 38.5% (5/13) PSA: 47% (9/19) PFS and OS not reported	Grade 3 neutropenia (3), Thromboembolism (1)

Definitions: **N=**: Total patients reported on study. **OR**: Overall Response (partial responses +complete responses). OR is only available for those patients with measurable disease and thus may report less patients than the total study number (N=). **PSA**: >50% decline from baseline. **mPFS**: median progression free survival. **mOS**: is median overall survival. **Doc-resistant**: patients had progressed on prior docetaxel therapy. When possible, grade 3 and 4 toxicity was limited to toxicity that was thought to be drug-related. **mTTF**: median time to failure.