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Targeting angiogenesis for the treatment of prostate cancer

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Abstract

Introduction—While multiple therapies exist that prolong the lives of men with advanced prostate cancer, none are curative. This had led to a search to uncover novel targets for prostate cancer therapy, distinct from those of traditional hormonal approaches, chemotherapies, immunotherapies and bone-targeting approaches. The process of tumor angiogenesis is one target that is being exploited for therapeutic gain.

Areas covered—The most promising anti-angiogenic approaches for treatment of prostate cancer, focusing on clinical development of selected agents. These include VEGF-directed therapies, tyrosine kinase inhibitors, tumor-vascular disrupting agents, immunomodulatory drugs and miscellaneous anti-angiogenic agents. While none of these drugs have yet entered the market for the treatment of prostate cancer, several are now being tested in Phase III registrational trials.

Expert opinion—The development of anti-angiogenic agents for prostate cancer has met with several challenges. This includes discordance between traditional prostate-specific antigen responses and clinical responses, which have clouded clinical trial design and interpretation, potential inadequate exposure to anti-angiogenic therapies with premature discontinuation of study drugs and the development of resistance to anti-angiogenic monotherapies. These barriers will hopefully be overcome with the advent of more potent agents, the use of dual angiogenesis inhibition and the design of more informative clinical trials.

Keywords

angiogenesis; bevacizumab; cabozantinib; clinical trials; drug development; itraconazole; lenalidomide; prostate cancer; sunitinib; tasquinimod; vadimezan

1. Introduction

Prostate cancer is the most common non-cutaneous malignancy in men in the USA and Europe, and is responsible for the second largest number of cancer-related deaths after lung cancer [1]. Although there are now many effective therapies that are able to extend the life

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Declaration of interest

ES Antonarakis has served as a consultant for Sanofi-Aventis. MA Carducci has served as a consultant for Amgen, Astellas, AstraZeneca, Johnson & Johnson, Genentech, Novartis, Pfizer and Sanofi-Aventis.

of patients with advanced prostate cancer (including hormonal approaches, chemotherapies, immunotherapies and bone-targeting approaches) [2], none of these modalities are curative. For this reason, there has been continued interest in identifying additional therapies exploiting alternative targets or pathways in an effort to expand the currently available treatment options for men with advanced prostate cancer. To this end, the notion of targeting prostate cancer by inhibiting tumor angiogenesis has given rise to a new class of antineoplastic agents: the angiogenesis inhibitors.

Since the landmark discovery that tumor blood vessels are required for cancers to grow and proliferate [3], there has been intense preclinical and clinical work to attempt to exploit this process for cancer therapeutics. While this approach has already yielded fruit for several cancer types, including renal cell carcinoma [4] and others, the role of angiogenesis inhibition in prostate cancer remains more questionable. This has been due, in part, to the disappointing negative results of a large Phase III study evaluating the prototype antiangiogenic agent, bevacizumab, when combined with standard chemotherapy in men with metastatic prostate cancer [5]. Two additional Phase III trials, examining sunitinib and lenalidomide, also failed to meet their primary endpoints [6,7]. However, there is no question that some prostate cancer patients do benefit from angiogenesis inhibitors (even when used as monotherapies), suggesting that work still needs to be done to identify predictive biomarkers of drug activity. In addition, a new wave of antiangiogenic drugs (such as the novel tyrosine kinase inhibitor, cabozantinib) has rekindled interest in this therapeutic approach.

Angiogenesis is a complex process involving multiple regulatory pathways, pro- and anti-angiogenic factors, and endothelial cell activation [8]. It is thought that the hypoxic tumor microenvironment stimulates the production of angiogenic cytokines, such as VEGF and basic fibroblast growth factor (bFGF), among others. In addition, there are naturally occurring antiangiogenic factors, such as endostatin and angiostatin, which interact with the proangiogenic factors to determine the overall angiogenic potential of the tumor microenvironment (Figure 1) [9]. Ample preclinical and clinical studies have demonstrated that blocking angiogenesis can slow tumor progression and metastasis [10]. Angiogenesis can be blocked by multiple mechanisms: by inhibiting proangiogenic factors directly, by inhibiting the receptors of proangiogenic factors, by raising the levels of endogenous antiangiogenic factors, or by killing tumor-related vascular endothelial cells themselves [11]. In this review, we discuss several of the most promising antiangiogenic strategies currently being investigated in the clinical arena for the treatment of prostate cancer (Table 1), with a focus on metastatic castration-resistant prostate cancer (CRPC).

2. VEGF-directed agents

2.1 Bevacizumab

Bevacizumab is a monoclonal antibody targeting the human VEGF ligand, and is currently FDA-approved for four tumor types. In prostate cancer, elevated concentrations of plasma VEGF have been correlated with advanced clinical stage and decreased survival [12]. Additionally, antibodies to VEGF slow tumor proliferation in prostate cancer xenograft models, especially when combined with chemotherapy [13]. In clinical trials, while the

single-agent activity of bevacizumab in men with prostate cancer is disappointing [14], more promising results were seen in a Phase II study of men with metastatic CRPC who received bevacizumab combined with docetaxel and estramustine chemotherapy [15]. In that study, 75% of men achieved significant prostate-specific antigen (PSA) declines while almost 60% of patients had partial radiographic responses. Encouraging results were also observed in a second Phase II study combining bevacizumab with docetaxel in a docetaxel-refractory population, where the objective response rate was 37% [16].

These results led to the conduct of a pivotal Phase III trial (CALGB 90401) evaluating docetaxel plus either bevacizumab or placebo in 1050 men with metastatic CRPC who had not previously received chemotherapy. Disappointingly, although an improvement in progression-free survival was seen in the docetaxel-bevacizumab arm of this study (9.9 versus 7.5 months, $p < 0.0001$), this did not translate into an overall survival advantage (22.6 versus 21.5 months, $p = 0.18$) [5]. These results do not necessarily indicate that bevacizumab may never have a role in the treatment of CRPC, as much of this failure may be explained by an imbalance of treatment-related toxicities (i.e., cardiovascular events, neutropenic complications) in this older population with multiple comorbidities. To this end, it was reported that the presence and number of comorbidities (e.g., cardiovascular disease, hypertension, diabetes, renal disease, liver disease) among patients in the CALGB 90401 trial significantly correlated with survival, and that there was an increase in the average number of comorbidities in the docetaxel-bevacizumab arm [17]. Another explanation for the discrepancy between progression-free survival and overall survival results may relate to an inadequate duration of bevacizumab exposure; because men discontinued bevacizumab at the time of biochemical or radiographic progression, the full potential effect of this agent on survival may not have been realized. Future development of this drug may focus on combining it with other classes of angiogenesis inhibitors or other chemotherapeutic agents whose toxicities do not overlap with those of bevacizumab. Alternatively, evaluation of serological markers from men treated on the CALGB 90401 trial may uncover a subset of patients that derive a survival advantage from using bevacizumab.

2.2 Aflibercept

An alternative VEGF-directed strategy makes use of VEGF decoy receptors (VEGF-trap) to saturate circulating VEGF ligand, preventing it from binding to its natural receptor. The lead compound in this class is aflibercept, a recombinant decoy fusion protein of VEGF receptors-1 and -2 and the Fc fragment of IgG1 [18]. In a Phase I/II study of intravenous aflibercept combined with docetaxel in heavily-pretreated patients with advanced solid tumors [19], the partial response rate was 9%, while 59% of patients demonstrated stable disease. Toxicities of this combination included neutropenia, hypertension, proteinuria, epistaxis, and dysphonia. A multicenter, placebo-controlled Phase III trial of docetaxel with or without aflibercept for men with metastatic CRPC is currently underway (NCT00519285) [20], with overall survival selected as the primary outcome measure (Table 2). Notably, aflibercept was recently shown to extend survival in patients with metastatic colorectal cancer when added to combination chemotherapy [21].

3. Tyrosine kinase inhibitors

3.1 Sunitinib

Tyrosine kinase inhibition is an alternative mechanism by which cancers can be targeted [22]. The development of drugs that inhibit the intracellular ATP-binding domain of the VEGF receptors has led to this new class of antineoplastic agents. Sunitinib is an oral non-selective tyrosine kinase inhibitor (TKI) that blocks VEGFR-2 and platelet-derived growth factor receptor beta (PDGFR β), as well as FLT-3 and KIT. In initial Phase II studies, sunitinib produced some partial radiographic responses (~ 10%) with minimal effect on PSA levels in men with both chemotherapy-naïve and docetaxel-pretreated metastatic CRPC [23,24]. In addition, a single-arm Phase I/II study of docetaxel plus sunitinib demonstrated tolerability and a reasonable degree of clinical activity in the first-line setting (42% objective response rate; 56% PSA response rate), with more than 85% of men surviving 1 year [25]. However, a definitive randomized Phase III study comparing single-agent sunitinib versus placebo in 872 patients with docetaxel-refractory metastatic CRPC was unable to demonstrate an overall survival improvement (13.1 versus 12.8 months; $p = 0.58$), even though there was a progression-free survival benefit favoring the sunitinib arm (5.6 versus 3.7 months; $p = 0.008$) [6]. This result indicates that sunitinib monotherapy may be insufficient to promote clinical benefit in an unselected patient population. Also, one potential reason for the failure of this trial may relate to the fact that sunitinib was administered at a dose of 37.5 mg per day (continuously), instead of at the usual dose of 50 mg per day (4 weeks on, 2 weeks off).

3.2 Sorafenib

Another non-selective antiangiogenic TKI is sorafenib, an agent which inhibits VEGFR-2 and -3, as well as PDGFR β and RAF. In several Phase II studies involving men with metastatic CRPC (both before and after docetaxel treatment), oral sorafenib monotherapy was shown to stabilize radiological progression and even caused regression of bone and soft-tissue metastases in some patients (< 10%), but without inducing significant PSA declines [26–28]. This discordance between objective tumor responses and PSA responses is reminiscent of the clinical data with sunitinib; whether this phenomenon is a class effect of VEGF receptor TKIs is currently unclear. Encouragingly, updated overall survival results from the most mature Phase II trial showed a median survival of 18 months [28], which is notable because the vast majority of men on this study had docetaxel-refractory disease. New trials evaluating sorafenib in early prostate cancer and/or in combination with hormone therapy and chemotherapy are currently underway (Table 2), but the Phase III development of this agent is uncertain at this time.

3.3 Cediranib

Cediranib is a more selective antiangiogenic TKI agent that inhibits only VEGFR-1 and -2, and has been shown to delay the growth of bone and brain metastases as well as to improve survival in a prostate cancer mouse model [29]. A Phase I study of oral cediranib in men with metastatic CRPC established a maximum tolerated dose of 20 mg, due to the occurrence of grade-3 muscle weakness and fatigue [30]. Interestingly, 1 out of 19 patients in that study had an objective tumor response while 3 out of 19 men had > 50% PSA

declines (which occurred after discontinuation of cediranib, clouding the use of PSA as a marker of antitumor activity with this agent). In a separate Phase II study of docetaxel-refractory patients, single-agent cediranib produced an objective response rate of 17%, while PSA levels did not correlate with clinical benefit [31]. Common toxicities of cediranib included hypertension, fatigue and dysphonia. Cediranib is currently being tested in a Phase II study where it is being given with or without the oral Src inhibitor dasatinib in patients with metastatic docetaxel-refractory CRPC (NCT01260688) [32]. The primary endpoint of this study is progression-free survival, defined by clinical/radiographic criteria but not by PSA criteria (Table 2).

3.4 Cabozantinib

An alternative target that has received renewed attention is the MET protein, a transmembrane receptor whose only known ligand is hepatocyte growth factor (HGF). Aberrant activation or overexpression of MET is a common event in prostate cancer (especially in castration-resistant bone metastases), and is associated with proliferation, invasion and angiogenesis [33,34]. Moreover, androgen suppression has been shown to promote increased MET expression [35].

Cabozantinib (XL184) is a potent oral inhibitor of MET and VEGFR-2 that has shown significant anti-angiogenic, anti-proliferative, and anti-invasive activity in preclinical systems [36]. Results from a randomized discontinuation Phase II study in 168 men with metastatic CRPC who had received up to one prior chemotherapy revealed objective tumor responses in approximately 10% of patients with measurable disease (74% of men showed some degree of tumor regression), and bone scan improvements in a remarkable 76% of men with osseous metastases, which was often accompanied by pain reductions (64% of patients) [37]. In addition, treatment with cabozantinib improved serum markers of bone resorption and bone formation in the majority of patients. Toxicities with this agent included fatigue, diarrhea, anorexia, emesis, hypertension and hand-foot syndrome. While the 12-week response rates, particularly in the bone, are striking (including some complete resolutions of skeletal abnormalities on bone scan), the lack of robust PSA responses and the uncertainty over the durability of these results will require confirmatory trials to assess the overall clinical benefit of this agent as well as the optimal dose for long-term use. Further investigation of this agent's activity in the bone using novel imaging techniques (^{18}F -positron-emission tomography (PET)) or pharmacodynamic studies are also being considered to further understand how this drug controls osseous metastatic disease. A pivotal randomized Phase III trial comparing cabozantinib against mitoxantrone chemotherapy in heavily pretreated patients with metastatic CRPC is currently underway (Table 2), and may serve as the regulatory trial for this agent in prostate cancer. Notably, this trial has chosen to evaluate pain responses, and not overall survival, as its primary efficacy endpoint.

4. Tumor-vascular-disrupting agents

4.1 Vadimezan

A different anti-angiogenic strategy involves the use of agents that directly act against established tumor blood vessels, disrupting vascular endothelial cells and causing a range of subsequent antivascular effects [38]. The prototype in this class of drugs is 5,6-dimethylxanthenoine-4-acetic acid (vadimezan), which has been shown to act synergistically with docetaxel in human prostate cancer xenografts [39]. In a multicenter randomized Phase II trial of docetaxel with or without intravenous vadimezan in 74 men with metastatic CRPC who had not received prior chemotherapy, > 30% PSA declines were observed in 37 and 59% of patients in the control and interventional arms respectively, while radiographic response rates were 9 and 23% respectively [40]. However, there were no significant differences in progression-free survival (8.4 versus 8.7 months; $p = 0.58$) or overall survival (17.2 versus 17.0 months; $p = 0.42$) between the two treatment arms. Notable adverse events with vadimezan included infusion-site pain, neutropenia and cardiac toxicities (supraventricular tachycardia, myocardial ischemia). While there are currently no ongoing Phase III trials of vadimezan in prostate cancer, the drug is now being tested in the Phase III setting in lung cancer.

5. Antiangiogenic/immunomodulatory drugs

5.1 Thalidomide

Thalidomide is an oral compound with observed antitumor activity across several malignancies. While its mechanism of action remains incompletely understood, thalidomide and its analogues (lenalidomide, pomalidomide) appear to inhibit angiogenesis by modulating the PDGFR β pathway [41], preventing secretion of VEGF and bFGF from tumor and stromal cells, as well as inhibiting endothelial cell migration and adhesion [42]. In addition to their antiangiogenic properties, thalidomide and its analogs have immunomodulatory effects including T-cell co-stimulation, regulatory T-cell inhibition, and NK cell activation [43,44].

Phase I/II studies using single-agent thalidomide in CRPC patients have yielded modest results with low PSA response rates (10 – 15%) [45,46]. However, in a randomized Phase II trial of weekly docetaxel with or without thalidomide in men with chemotherapy-naïve CRPC, PSA responses, progression-free survival, and overall survival trended in favor of the combination arm [47]. In an updated analysis from this trial, overall survival was statistically superior in the thalidomide arm (25.9 versus 14.7 months; $p = 0.04$) [48]. However, toxicities with thalidomide can be troublesome and include deep venous thrombosis (which may be mitigated by aspirin or low-molecular-weight heparin), sedation, neuropathy, constipation and fatigue. Notably, a Phase II trial using a three-drug combination of docetaxel, thalidomide and bevacizumab showed impressive PSA response rates in the 90% range, although significant neurotoxicity and neutropenia were prohibitive with this combination [49]. Future studies using this class of agents in men with CRPC will probably focus on lenalidomide over thalidomide, due to the milder toxicity profile and lack

of neurological sequelae with lenalidomide, especially since these agents may be administered in combination or in sequence with docetaxel (which itself can be neurotoxic).

5.2 Lenalidomide

Lenalidomide was developed to build on thalidomide's activity while improving on its side effect profile [50]. To this end, lenalidomide causes less neurotoxicity and sedation than thalidomide (but more myelosuppression). Evaluation of lenalidomide in advanced prostate cancer has focused mainly on combination trials. In an initial Phase I study, lenalidomide was administered together with docetaxel in men with metastatic CRPC [51]. Of 31 total patients 48% had PSA responses, and among patients with measurable disease 39% had partial radiographic responses. In a second Phase I/II study, lenalidomide was given together with GM-CSF in patients with CRPC, resulting in 24% of men achieving PSA reductions [52]. Another Phase II trial examined the combination of lenalidomide and ketoconazole in men with CRPC [53]. In that study, 78% of patients experienced PSA responses while 25% of those with measurable disease had partial objective responses. A fourth study tested the combination of lenalidomide with weekly paclitaxel in men with docetaxel-refractory CRPC [54], but the toxicity of this combination proved to be prohibitive. In general, the most common adverse events attributed to lenalidomide in these four studies included fatigue, dizziness, rash, pruritus, diarrhea, neutropenia and thrombocytopenia. These encouraging early-phase results prompted the design of a large Phase III study (NCT00988208) [55] that randomized 1015 men with chemotherapy-naïve CRPC to receive docetaxel plus lenalidomide or docetaxel plus placebo. Disappointingly, this study failed to meet its primary survival endpoint [7], calling into question the role of lenalidomide in men with advanced prostate cancer.

Lenalidomide was also evaluated in 60 men with non-metastatic biochemically-recurrent prostate cancer. In this trial, patients were randomized to receive either 25 mg/day (high-dose) or 5 mg/day (low-dose) of lenalidomide (3 weeks on, 1 week off) [56]. Encouragingly, men receiving high-dose lenalidomide had a significantly greater reduction in median post-treatment PSA slope than men receiving low-dose lenalidomide (0.172 versus 0.033, $p = 0.005$), suggesting that this agent modulates PSA kinetics in a dose-dependent manner. In addition, PSA progression-free survival after 6 months on study was 73% in the low-dose arm and 85% in the high-dose arm, compared with an estimated 6-month PSA progression-free rate of about 25% in an untreated historical control group [57], suggesting that both doses may have activity. Intriguingly, clinical benefit from lenalidomide in this patient population appeared to correlate with decreased serum IL-8 levels as well as the generation of novel anti-PSA antibodies in response to lenalidomide [58]. A larger three-arm randomized study comparing low-dose and high-dose lenalidomide against placebo in men with biochemically-recurrent prostate cancer is currently being designed (Table 2), and will use progression-free survival as its primary endpoint.

6. Miscellaneous angiogenesis inhibitors

6.1 Tasquinimod

Another angiogenesis-inhibiting agent that has received recent attention is the oral quinoline-3-carboxamide derivative, tasquinimod. Although the anti-angiogenic effects of this drug have been amply demonstrated in several *in vitro* and *in vivo* prostate cancer models [59], the exact mechanism of action of this agent remains elusive and may be related to induction of the endogenous antiangiogenic factor, thrombospondin-1. Another proposed mechanism of action of tasquinimod involves inhibition of S100A9, an immunomodulatory protein involved in cell cycle progression and differentiation as well as recruitment of tumor-infiltrating myeloid-derived suppressor cells [60]. In human prostate cancer xenograft models, tasquinimod demonstrated anti-tumor activity without an appreciable effect on PSA levels [61].

Tasquinimod was well tolerated in clinical Phase I studies of men with CRPC [62]; dose-limiting toxicities included sinus tachycardia and asymptomatic amylase elevations. Impressively, a randomized double-blind placebo-controlled Phase II study involving 201 patients with chemotherapy-naïve metastatic CRPC met its prespecified primary endpoint and demonstrated that patients receiving oral tasquinimod had a median progression-free survival of 7.6 months versus 3.3 months in those receiving placebo ($p = 0.004$) [63]. Clinical activity was independent of PSA responses, and PSA parameters were not used to define disease progression. Drug-related adverse events in this study included gastrointestinal disorders, fatigue, musculoskeletal pain and asymptomatic elevations of pancreatic enzymes and inflammatory markers. Rare but serious toxicities were arrhythmias, heart failure, myocardial infarction, stroke and deep vein thrombosis. Following from these encouraging results, a multi-center randomized Phase III trial of tasquinimod versus placebo in men with chemotherapy-untreated metastatic CRPC has been activated and plans to accrue 1200 patients (NCT01234311) [64]. This study is powered to detect an improvement in both progression-free survival and overall survival (Table 2).

6.2 Itraconazole

A surprising addition to the anti-angiogenic drug family is the antifungal agent, itraconazole. In an effort to uncover new functions for existing compounds [65], a drug library was screened for agents that inhibit human endothelial cells *in vitro*. One of the hits from this screen was itraconazole, which was found to inhibit endothelial cell proliferation much more potently than all other azole antifungal drugs [66]. Itraconazole was also shown to inhibit endothelial cell migration and chemotaxis, as well as capillary tube formation [67]. Although the drug's antiangiogenic target is uncertain, one study suggested that itraconazole inhibited mammalian target of rapamycin complex 1 (mTORC1) and mammalian target of rapamycin complex 2 (mTORC2) in endothelial cells by impairing cholesterol trafficking in these cells [68]. *In vivo*, itraconazole was found to inhibit new blood vessel formation in a mouse Matrigel model, to delay tumor growth in a castration-resistant xenograft mouse model (22Rv1), and to inhibit metastases in the AT6.3 prostate cancer mouse model [66]. Intriguingly, itraconazole was also discovered to be a potent inhibitor of Hedgehog (Hh) signaling, a developmental pathway that regulates epithelial-mesenchymal interactions, cell

proliferation, survival and angiogenesis [69]. To this end, *in vitro* studies showed that itraconazole inhibited proliferation of the Hh reporter cell line Shh-Light2, by preventing accumulation of Smoothed (Smo) in primary cilia of these cells [70]. In addition, itraconazole induced tumor growth inhibition in a mouse medulloblastoma model (Ptch^{+/-} p53^{-/-}) with constitutive overactivation of Hh signaling. In this murine allograft model, serum levels of itraconazole required for tumor inhibition were equivalent to those achieved in man using 600 mg of oral itraconazole daily [70].

Following on from these preclinical data, itraconazole has recently been evaluated in a randomized Phase II trial in men with chemotherapy-naïve metastatic CRPC [71]. In this study, 46 men were randomized to receive either low-dose (200 mg/day) or high-dose (600 mg/day) itraconazole on a continuous basis. The study met its primary endpoint, showing that PSA progression-free survival was prolonged in the high-dose arm (17.0 versus 11.9 weeks) as was radiographic progression-free survival (35.9 versus 11.9 weeks). In addition, while there were no PSA responses in the low-dose arm, PSA responses were seen in 14% of men in the high-dose arm, although there was some discordance between PSA reductions and clinical benefit. In addition, 62% of men who had unfavorable baseline circulating tumor cell counts (≥ 5 CTCs/7.5 ml blood) converted to a favorable CTC count (< 5 CTCs/7.5 ml blood) after itraconazole treatment [71]. Importantly, itraconazole's activity was not mediated by androgen suppression (as is the case with ketoconazole). Common toxicities of high-dose itraconazole included fatigue, nausea, anorexia and rash, as well as a mineralocorticoid syndrome consisting of hypokalemia, hypertension and edema. A separate Phase II study (NCT01450683) [72] of itraconazole in men with docetaxel-pretreated CRPC is currently underway (Table 2).

7. Expert opinion

Angiogenesis appears to play an important role in prostate cancer maintenance and progression, with several studies showing correlations between markers of angiogenesis and higher Gleason score, presence of metastatic disease and clinical outcomes. In addition, myriad preclinical studies have demonstrated the putative benefits of angiogenesis inhibition. However, while anti-angiogenic agents would seem like a promising addition to prostate cancer therapies, challenges in clinical trial design and interpretation have prevented these drugs from entering the marketplace and clinical practice.

One of these challenges relates to the discordance between PSA trends and clinical benefit from these drugs. For instance, studies of sunitinib, cabozantinib, tasquinimod and itraconazole have all shown that clinical responses do not always correlate with PSA declines, while in certain cases PSA can even rise in the face of documented tumor regressions. To address this pitfall, the Prostate Cancer Working Group has proposed specific clinical trial endpoints to be applied to cytostatic therapies (including angiogenesis inhibitors) which emphasize clinical events [73]. For example, these guidelines stress the importance of radiographic and/or symptomatic progression when making treatment decisions, and discourage the isolated use of PSA to define progression or discontinue treatment. These recommendations are currently being followed in the pivotal Phase III trials of tasquinimod and cabozantinib, both of which will disregard PSA changes in

defining their primary endpoints (progression-free survival and pain improvement, respectively). In the tasquinimod study, for instance, disease progression is defined by clinical and radiographic criteria but not by PSA elevations.

A second potential reason for the failure of certain pivotal trials to show a meaningful treatment benefit may have to do with premature discontinuation of the anti-angiogenic agents. For example, in the Phase III study of bevacizumab (CALGB 90401), study drug was discontinued at the time of PSA progression. This may explain, at least partially, why such a large progression-free survival advantage was observed without any appreciable overall survival benefit. Use of the clinical trial guidelines discussed above [73] may have limited premature discontinuation of therapy in this trial. Similar scenarios may have existed in the Phase III sunitinib and lenalidomide studies. This consideration raises the issue of maintenance anti-angiogenic therapy, continued beyond disease progression in men with advanced prostate cancer. One cannot help to wonder if use of a maintenance schedule of bevacizumab may have led to a survival benefit in the CALGB 90401 trial. Notably, the role of bevacizumab maintenance has been suggested in other malignancies, including advanced lung and ovarian cancers. However, a maintenance approach would certainly increase the cost of therapy, and would have significant pharmacoeconomic implications. It may also increase the long-term toxicities from these agents.

One final explanation for the suboptimal efficacy of angiogenesis inhibitors in prostate cancer may relate to intrinsic or adaptive mechanisms of resistance to anti-angiogenic monotherapies. This may imply that some angiogenic pathways may be redundant, or that tumors may develop the ability to progress independently of neovascularization. In order to try to overcome such resistance mechanisms, the angiogenesis process itself could be targeted by multiple agents (e.g., dual angiogenesis inhibition), or angiogenesis could be targeted in addition to other oncogenic pathways (e.g., dual pathway inhibition). Dual inhibition could potentially be achieved by a single agent with multiple drug targets (e.g., cabozantinib, which inhibits VEGFR-2 as well as MET), or by using multiple agents (e.g., the combination of bevacizumab, thalidomide and docetaxel). However, the approach of combining multiple drugs will require extreme caution to avoid unexpected toxicities, and various strategies exist to mitigate the potential toxicity of anti-angiogenic combinations. These include monitoring pharmacodynamic endpoints rather than escalating to a maximum tolerated dose of each drug, or limiting the exposure of a drug by restricting its administration to a short pulse at a critical point in the treatment cycle (i.e., timed-sequential therapy).

In conclusion, continued enthusiasm for anti-angiogenesis therapies in prostate cancer has been warranted by signs of clinical activity with several agents, although a home run has not yet been achieved with any one particular drug to date. The recent discovery of more active agents, coupled with new approaches to designing informative clinical trials, should give us hope that angiogenesis inhibitors will soon enter the therapeutic arsenal for men with advanced prostate cancer. Identifying predictive biomarkers of drug response (or resistance) to anti-angiogenic agents remains a challenge of the future.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin.* 2011; 61:212–36. [PubMed: 21685461]
2. Antonarakis ES, Eisenberger MA. Expanding treatment options for metastatic prostate cancer. *N Engl J Med.* 2011; 364:2055–8. [PubMed: 21612475]
3. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med.* 1971; (21):1182–6. [PubMed: 4938153]
4. Molina AM, Motzer RJ. Clinical practice guidelines for the treatment of metastatic renal cell carcinoma: today and tomorrow. *Oncologist.* 2011; 16:45–50. [PubMed: 21346039]
- 5•. Kelly WK, Halabi S, Carducci MA, et al. A randomized double-blinded placebo controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with castration-resistant prostate cancer (CALGB 90401). *J Clin Oncol.* 2012 In press This is the pivotal Phase III trial of docetaxel with or without bevacizumab for men with metastatic castration-resistant prostate cancer.
- 6••. Dror Michaelson M, Oudard S, Ou Y, et al. Randomized, placebo-controlled, phase III trial of sunitinib in combination with prednisone versus prednisone alone in men with progressive metastatic castration-resistant prostate cancer. *J ClinOncol.* 2011; 29(Suppl):abstract 4515. This is the pivotal Phase III trial of sunitinib for men with docetaxel-refractory metastatic castration-resistant prostate cancer.
7. Celgene will discontinue phase III Mainsail trial in castrate-resistant prostate cancer. Boudry, Switzerland: Celgene Corp; 2011. Available from: <http://ir.celgene.com/phoenix.zhtml?c=111960&p=irol-newsArticle&ID=1633148&highlight> [Last accessed 27 February 2012]
8. Li Y, Cozzi PJ. Angiogenesis as a strategic target for prostate cancer therapy. *Med Res Rev.* 2010; 30:23–66. [PubMed: 19536866]
9. Weis SM, Cheresch DA. Tumor angiogenesis: molecular pathways and therapeutic targets. *Nat Med.* 2011; 17:1359–70. [PubMed: 22064426]
10. Carmeliet P, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. *Nature.* 2011; 473:298–307. [PubMed: 21593862]
11. Kluetz PG, Figg WD, Dahut WL. Angiogenesis inhibitors in the treatment of prostate cancer. *Expert Opin Pharmacother.* 2010; 11:233–47. [PubMed: 20088745]
12. George DJ, Halabi S, Shepard TF, et al. Prognostic significance of plasma vascular endothelial growth factor levels in patients with hormone-refractory prostate cancer treated on Cancer and Leukemia Group B 9480. *Clin Cancer Res.* 2001; 7:1932–6. [PubMed: 11448906]
13. Sweeney P, Karashima T, Kim SJ, et al. Anti-vascular endothelial growth factor receptor 2 antibody reduces tumorigenicity and metastasis in orthotopic prostate cancer xenografts via induction of endothelial cell apoptosis and reduction of endothelial cell matrix metalloproteinase type 9 production. *Clin Cancer Res.* 2002; 8:2714–24. [PubMed: 12171905]
14. 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 J.* 2001; 3:65–70.
15. Picus J, Halabi S, Kelly WK, et al. A Phase II study of estramustine, docetaxel, and bevacizumab in men with castrate-resistant prostate cancer: results from Cancer and Leukemia Group B Study 90006. *Cancer.* 2011; 117:526–33. [PubMed: 20862750]
16. Di Lorenzo G, Figg WD, Fossa SD, et al. Combination of bevacizumab and docetaxel in docetaxel-pretreated hormone-refractory prostate cancer: a Phase 2 study. *Eur Urol.* 2008; 54:1089–96. [PubMed: 18276061]
17. Halabi S, Kelly WK, George DJ, et al. Comorbidities predict overall survival in men with metastatic castrate-resistant prostate cancer. *J Clin Oncol.* 2011; 29(Suppl):abstract 189.

18. Chu QS. Aflibercept: an alternative strategy for inhibiting tumour angiogenesis by vascular endothelial growth factors. *Expert Opin Biol Ther.* 2009; 9:263–71. [PubMed: 19236257]
19. Isambert N, Freyer G, Zanetta S, et al. A phase I dose escalation and pharmacokinetic (PK) study of intravenous aflibercept (VEGF trap) plus docetaxel in patients with advanced solid tumors: preliminary results. *J Clin Oncol.* 2008; 26(Suppl):abstract 3599.
20. Sanofi-Aventis, Regeneron Pharmaceuticals. Aflibercept in Combination with Docetaxel in Metastatic Androgen Independent Prostate Cancer. *ClinicalTrials.gov.* NCT00519285. Available from: <http://clinicaltrials.gov/ct2/show/NCT00519285?term=NCT00519285&rank=1>
21. Tabernero, J.; Van, Cutsem E.; Lakomy, R., et al. Results from VELOUR, a phase III study of aflibercept versus placebo in combination with FOLFIRI for the treatment of patients with previously treated metastatic colorectal cancer [abstract LBA6]. *ECCO-ESMO European Multidisciplinary Congress*; 2011.
22. Takeuchi K, Ito F. Receptor tyrosine kinases and targeted cancer therapeutics. *Biol Pharm Bull.* 2011; 34:1774–80. [PubMed: 22130229]
23. Dror Michaelson M, Regan MM, Oh WK, et al. Phase II study of sunitinib in men with advanced prostate cancer. *Ann Oncol.* 2009; 20:913–20. [PubMed: 19403935]
24. Sonpavde G, Periman PO, Bernold D, et al. Sunitinib malate for metastatic castrate-resistant prostate cancer following docetaxel-based chemotherapy. *Ann Oncol.* 2010; 21:319–24. [PubMed: 19633050]
25. Zurita AJ, George DJ, Shore ND, et al. Sunitinib in combination with docetaxel and prednisone in chemotherapy-naïve patients with metastatic, castration-resistant prostate cancer: a phase I/II clinical trial. *Ann Oncol.* 2011 published online 5 august 2011. 10.1093/annonc/mdr349
26. Steinbild S, Mross K, Frost A, et al. A clinical phase II study with sorafenib in patients with progressive hormone-refractory prostate cancer: a study of the CESAR Central European Society for Anticancer Drug Research-EWIV. *Br J Cancer.* 2007; 97:1480–5. [PubMed: 18040273]
27. Dahut WL, Scripture C, Posadas E, et al. A Phase II clinical trial of sorafenib in androgen-independent prostate cancer. *Clin Cancer Res.* 2008; 14:209–14. [PubMed: 18172272]
28. Aragon-Ching JB, Jain L, Gulley JL, et al. Final analysis of a phase II trial using sorafenib for metastatic castration-resistant prostate cancer. *BJU Int.* 2009; 103:1636–40. [PubMed: 19154507]
29. Yin JJ, Zhang L, Munasinghe J, et al. Cediranib/AZD2171 inhibits bone and brain metastasis in a preclinical model of advanced prostate cancer. *Cancer Res.* 2010; 70:8662–73. [PubMed: 20959486]
30. Ryan CJ, Stadler WM, Roth B, et al. Phase I dose escalation and pharmacokinetic study of AZD2171, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinase, in patients with hormone refractory prostate cancer. *Invest New Drugs.* 2007; 25:445–51. [PubMed: 17458505]
31. Adelberg, D.; Karakunnel, J.; Gulley, J., et al. A phase II study of cediranib in post-docetaxel castration resistant prostate cancer [abstract 41]. *ASCO Genitourinary Cancers Symposium*; 2010.
32. Princess Margaret Hospital, Canada, National Cancer Institute (NCI). Cediranib Maleate With or Without Dasatinib in Patients With Hormone-Resistant Prostate Cancer Resistant to Treatment With Docetaxel. *ClinicalTrials.gov.* NCT01260688. Available from: <http://clinicaltrials.gov/ct2/show/NCT01260688?term=NCT01260688&rank=1>
33. Knudsen BS, Gmyrek GA, Inra J, et al. High expression of the Met receptor in prostate cancer metastasis to bone. *Urology.* 2002; 60:1113–17. [PubMed: 12475693]
34. Christensen JG, Burrows J, Salgia R. c-Met as a target for human cancer and characterization of inhibitors for therapeutic intervention. *Cancer Lett.* 2005; 225:1–26. [PubMed: 15922853]
35. Verras M, Lee J, Xue H, et al. The androgen receptor negatively regulates the expression of c-Met: implications for a novel mechanism of prostate cancer progression. *Cancer Res.* 2007; 67:967–75. [PubMed: 17283128]
36. Shojaei F, Lee JH, Simmons BH, et al. HGF/c-Met acts as an alternative angiogenic pathway in sunitinib-resistant tumors. *Cancer Res.* 2010; 70:10090–100. [PubMed: 20952508]
- 37•. Hussain M, Smith MR, Sweeney C, et al. Cabozantinib (XL184) in metastatic castration-resistant prostate cancer: results from a phase II randomized discontinuation trial. *J ClinOncol.* 2011;

- 29(Suppl):abstract 4516. This is the first trial, to our knowledge, to test cabozantinib in men with metastatic castration-resistant prostate cancer, showing striking responses in bone metastases.
38. McKeage MJ. The potential of DMXAA (ASA404) in combination with docetaxel in advanced prostate cancer. *Expert Opin Investig Drugs*. 2008; 17:23–9.
 39. McKeage MJ, Kelland LR. 5,6-dimethylxanthenoine-4-acetic acid (DMXAA) clinical potential in combination with taxane-based chemotherapy. *Am J Cancer*. 2006; 5:155–62.
 40. Pili R, Rosenthal MA, Mainwaring PN, et al. Phase II study on the addition of ASA404 (vadimezan; 5,6-dimethylxanthene-4-acetic acid) to docetaxel in CRMPC. *Clin Cancer Res*. 2010; 16:2906–614. [PubMed: 20460477]
 41. Ng SS, MacPherson GR, Gutschow M, et al. Antitumor effects of thalidomide analogs in human prostate cancer xenografts implanted in immunodeficient mice. *Clin Cancer Res*. 2004; 10:4192–7. [PubMed: 15217957]
 42. Li H, Raia V, Bertolini F, et al. Circulating endothelial cells as a therapeutic marker for thalidomide in combined therapy with chemotherapy drugs in a human prostate cancer model. *BJU Int*. 2008; 101:884–8. [PubMed: 18070197]
 43. Paravar T, Lee DJ. Thalidomide: mechanisms of action. *Int Rev Immunol*. 2008; 27:111–35. [PubMed: 18437602]
 44. Galustian C, Dalgleish A. Lenalidomide: a novel anticancer drug with multiple modalities. *Expert Opin Pharmacother*. 2009; 10:125–33. [PubMed: 19236186]
 45. Figg WD, Dahut W, Duray P, et al. A randomized Phase II trial of thalidomide, an angiogenesis inhibitor, in androgen-independent prostate cancer. *Clin Cancer Res*. 2001; 7:1888–93. [PubMed: 11448901]
 46. Drake MJ, Robson W, Mehta P, et al. An open-label phase II study of low-dose thalidomide in androgen-independent prostate cancer. *Br J Cancer*. 2003; 88:822–7. [PubMed: 12644816]
 47. Dahut WL, Gulley JL, Arlen PM, et al. Randomized Phase II trial of docetaxel plus thalidomide in androgen-independent prostate cancer. *J Clin Oncol*. 2004; 22:2532–9. [PubMed: 15226321]
 48. Figg W, Retter A, Steinberg S, Dahut W. In reply to: “Inhibition of angiogenesis: thalidomide or low-molecular-weight heparin?” *J Clin Oncol*. 2005; 23:2113–214. [PubMed: 15774812]
 49. Ning YM, Gulley JL, Arlen PM, et al. Phase II trial of bevacizumab, thalidomide, docetaxel, and prednisone in patients with metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2010; 28:2070–6. [PubMed: 20308663]
 50. Mitsiades CS, Mitsiades N. Lenalidomide. *Curr Opin Investig Drugs*. 2005; 5:635–47.
 51. Moss, R.; Mohile, S.; Shelton, G., et al. A phase I open-label study using lenalidomide and docetaxel in androgen-independent prostate cancer [abstract 89]. *ASCO Genitourinary Cancers Symposium*; 2007.
 52. Dreicer R, Garcia J, Smith S, et al. Phase I/II trial of GM-CSF and lenalidomide in patients with hormone refractory prostate cancer. *J Clin Oncol*. 2007; 25(Suppl):abstract 15515.
 53. Garcia JA, Triozzi P, Elson P, et al. Clinical activity of ketoconazole and lenalidomide in castrate progressive prostate carcinoma: preliminary results of a phase II trial. *J Clin Oncol*. 2008; 26(Suppl):abstract 5143.
 54. Mathew P, Tannir N, Tu SM, et al. A modular phase I study of lenalidomide and paclitaxel in metastatic castration-resistant prostate cancer following prior taxane therapy. *Cancer Chemother Pharmacol*. 2010; 65:811–15. [PubMed: 20052472]
 55. Celgene Corp. Study to Evaluate Safety and Effectiveness of Lenalidomide in Combination With Docetaxel and Prednisone for Patients With Castrate-Resistant Prostate Cancer (Mainsail). *ClinicalTrials.gov*. NCT00988208. Available from: <http://clinicaltrials.gov/ct2/show/NCT00988208?term=NCT00988208&rank=1>
 56. Keizman D, Zahurak M, Sinibaldi V, et al. Lenalidomide in nonmetastatic biochemically relapsed prostate cancer: results of a Phase I/II double-blinded, randomized study. *Clin Cancer Res*. 2010; 16:5269–76. This study showed that lenalidomide has activity in men with biochemically-recurrent prostate cancer after local therapy. [PubMed: 20978144]
 57. Antonarakis ES, Feng Z, Trock BJ, et al. The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. *BJU Int*. 2012; 109:32–9. [PubMed: 21777360]

58. Zabransky DJ, Smith HA, Thoburn CJ, et al. Lenalidomide modulates IL-8 and anti-prostate antibody levels in men with biochemically recurrent prostate cancer. *Prostate*. 2012; 72:487–98. [PubMed: 21748755]
59. Isaacs JT, Pili R, Qian DZ, et al. Identification of ABR-215050 as lead second generation quinoline-3-carboxamide anti-angiogenic agent for the treatment of prostate cancer. *Prostate*. 2006; 66:1768–78. [PubMed: 16955399]
60. Bjork P, Bjork A, Vogl T, et al. Identification of human S100A9 as a novel target for treatment of autoimmune disease via their binding to quinolinecarboxamides. *PLoS Biol*. 2009; 7:e97. [PubMed: 19402754]
61. Dalrymple SL, Becker RE, Isaacs JT. The quinoline-3-carboxamide anti-angiogenic agent, tasquinimod, enhances the anti-prostate cancer efficacy of androgen ablation and docetaxel without effecting serum PSA directly in human xenografts. *Prostate*. 2007; 67:790–7. [PubMed: 17373719]
62. Bratt O, Haggman M, Ahlgren G, et al. Open-label, clinical phase I studies of tasquinimod in patients with castration-resistant prostate cancer. *Br J Cancer*. 2009; 101:1233–40. [PubMed: 19755981]
- 63•. Pili R, Haggman M, Stadler WM, et al. Phase II randomized, double-blind, placebo-controlled study of tasquinimod in men with minimally symptomatic metastatic castrate-resistant prostate cancer. *J Clin Oncol*. 2011; 29:4022–8. This study showed that oral tasquinimod has activity in men with chemotherapy-naïve metastatic castration-resistant prostate cancer. [PubMed: 21931019]
64. Active Biotech AB. A Study of Tasquinimod in Men with Metastatic Castrate Resistant Prostate Cancer. ClinicalTrials.gov. NCT01234311. Available from: <http://clinicaltrials.gov/ct2/show/NCT01234311?term=NCT01234311&rank=1>
65. Chong CR, Sullivan DJ Jr. New uses for old drugs. *Nature*. 2007; 448:645–6. [PubMed: 17687303]
66. Chong CR, Xu J, Lu J, et al. Inhibition of angiogenesis by the antifungal drug itraconazole. *ACS Chem Biol*. 2007; 2:263–70. [PubMed: 17432820]
67. Aftab BT, Dobromilskaya I, Liu JO, Rudin CM. Itraconazole inhibits angiogenesis and tumor growth in non-small cell lung cancer. *Cancer Res*. 2011; 71:6764–72. [PubMed: 21896639]
68. Xu J, Dang Y, Ren YR, Liu JO. Cholesterol trafficking is required for mTOR activation in endothelial cells. *Proc Natl Acad Sci USA*. 2010; 107:4764–9. [PubMed: 20176935]
69. Karhadkar SS, Bova GS, Abdallah N, et al. Hedgehog signaling in prostate regeneration, neoplasia and metastasis. *Nature*. 2004; 431:707–12. [PubMed: 15361885]
70. Kim J, Tang JY, Gong R, et al. Itraconazole, a commonly used antifungal that inhibits Hedgehog pathway activity and cancer growth. *Cancer Cell*. 2010; 17:388–99. [PubMed: 20385363]
- 71•. Antonarakis ES, Heath EI, Smith DC, et al. A non-comparative randomized phase II study of two dose levels of itraconazole in men with metastatic castration-resistant prostate cancer (mCRPC): a DOD/PCCTC trial. *J Clin Oncol*. 2011; 29(Suppl):abstract 4532. This study showed that high-dose itraconazole has activity in men with chemotherapy-naïve metastatic castration-resistant prostate cancer.
72. Stanford University. Study of Itraconazole in Castration Resistant Prostate Cancer (CRPC) Post Docetaxel Chemotherapy. ClinicalTrials.gov. NCT01450683. Available from: <http://clinicaltrials.gov/ct2/show/NCT01450683?term=NCT01450683&rank=1>
73. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol*. 2008; 26:1148–59. [PubMed: 18309951]
74. Case Comprehensive Cancer Center. Temsirolimus and Bevacizumab in Hormone-Resistant Metastatic Prostate Cancer That Did Not Respond to Chemotherapy. ClinicalTrials.gov. NCT01083368. Available from: <http://clinicaltrials.gov/ct2/show/NCT01083368?term=NCT01083368&rank=1>
75. Dana-Farber Cancer Institute, Genentech, Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Cancer Institute of New Jersey. Androgen Deprivation Therapy +/- Bevacizumab for PSA Recurrence of Prostate Cancer After Definitive Local Therapy.

ClinicalTrials.gov. NCT00776594. Available from: <http://clinicaltrials.gov/ct2/show/NCT00776594?term=NCT00776594&rank=1>

76. University of California (Irvine), Sanofi-Aventis. Trial of Taxotere Plus Sunitinib on Newly Diagnosed, Hormone Refractory, Metastatic Prostate Cancer. ClinicalTrials.gov. NCT00879619. Available from: <http://clinicaltrials.gov/ct2/show/NCT00879619?term=NCT00879619&rank=1>
77. Duke University, Pfizer, Sanofi-Aventis. Multimodality Phase II Study in Prostate Cancer. ClinicalTrials.gov. NCT00734851. Available from: <http://clinicaltrials.gov/ct2/show/NCT00734851?term=NCT00734851&rank=1>
78. Oncology Specialists, S.C. Sorafenib to Overcome Resistance to Systemic Chemotherapy in Androgen-independent Prostate Cancer. ClinicalTrials.gov. NCT00414388. Available from: <http://clinicaltrials.gov/ct2/show/NCT00414388?term=NCT00414388&rank=1>
79. University of Pennsylvania, National Cancer Institute (NCI). Sorafenib and Docetaxel in Treating Patients With Metastatic Prostate Cancer That Did Not Respond to Previous Hormone Therapy. ClinicalTrials.gov. NCT00589420. Available from: <http://clinicaltrials.gov/ct2/show/NCT00589420?term=NCT00589420&rank=1>
80. Barbara Ann Karmanos Cancer Institute, National Cancer Institute (NCI). Docetaxel and Prednisone With or Without Cediranib in Treating Patients With Metastatic Prostate Cancer That Did Not Respond to Hormone Therapy. ClinicalTrials.gov. NCT00527124. Available from: <http://clinicaltrials.gov/ct2/show/NCT00527124?term=NCT00527124&rank=1>
81. Smith, DC. Exelixis. Trial of Cabozantinib (XL184) in Castrate-Resistant Prostate Cancer Metastatic to Bone. ClinicalTrials.gov. NCT01428219. Available from: <http://clinicaltrials.gov/ct2/show/NCT01428219?term=NCT01428219&rank=1>
82. University of Pittsburgh, Ortho Biotech, Inc. Thalidomide and Doxil® in Patients With Androgen Independent Prostate Cancer (AIPC). ClinicalTrials.gov. NCT00307294. Available from: <http://clinicaltrials.gov/ct2/show/NCT00307294?term=NCT00307294&rank=1>
83. National Cancer Institute (NCI), National Institutes of Health Clinical Center (CC). A Phase II Trial of Bevacizumab, Lenalidomide, Docetaxel, and Prednisone (ART-P) for Treatment of Metastatic Castrate-Resistant Prostate Cancer. ClinicalTrials.gov. NCT00942578. Available from: <http://clinicaltrials.gov/ct2/show/NCT00942578?term=NCT00942578&rank=1>

Article highlights

- Bevacizumab improved progression-free survival but not overall survival in a pivotal Phase III study where it was combined with docetaxel in men with metastatic castration-resistant prostate cancer (CRPC). However, this does not mean that VEGF-directed therapies may not prove effective in other settings, and a Phase III study evaluating aflibercept (VEGF trap) is currently underway.
- Sunitinib, an oral non-selective VEGF receptor tyrosine kinase inhibitor, did not improve survival compared with placebo in a Phase III trial of men with docetaxel-refractory CRPC. However, other more selective VEGF receptor tyrosine kinase inhibitors (e.g., cediranib) may show more promise moving forward.
- Cabozantinib is a novel oral dual VEGFR-2 and MET inhibitor with impressive anti-tumor activity, especially in castration-resistant bone metastases. It is currently being evaluated in a pivotal Phase III trial in men with heavily pretreated CRPC, and will use pain response as its primary endpoint.
- Lenalidomide is a thalidomide analogue that functions both as an antiangiogenic agent and as an immunomodulatory drug. Although the addition of lenalidomide to docetaxel in men with metastatic CRPC did not improve overall survival, this agent may hold more promise in men with biochemically-recurrent non-metastatic prostate cancer.
- Tasquinimod is an oral quinoline derivative that inhibits S100A9 and increases endogenous thrombospondin-1 levels. Promising activity in a placebo-controlled randomized Phase II study has led to the launch of a global Phase III trial in men with metastatic CRPC.
- Itraconazole is an unexpected angiogenesis inhibitor that also blocks Hedgehog signaling. High doses of this agent (600 mg/day) appear to have activity in metastatic CRPC that is independent of androgen suppression.

This box summarizes key points contained in the article.

Figure 1. Simplified schematic of the angiogenesis pathway including key antiangiogenic targets and select inhibitory compounds
bFGF: Basic fibroblast growth factor; PDGF: Platelet-derived growth factor; PDGFR: Platelet-derived growth factor receptor.

Table 1

Selected angiogenesis inhibitors in prostate cancer therapy.

VEGF-directed agents	Bevacizumab Aflibercept
Tyrosine kinase inhibitors	Sunitinib Sorafenib Cediranib Cabozantinib
Tumor-vascular-disrupting agents	Vadimezan
Antiangiogenic/immunomodulatory drugs	Thalidomide Lenalidomide
Miscellaneous angiogenesis inhibitors	Tasquinimod Itraconazole

Table 2

Selected ongoing Phase II and III clinical trials of anti-angiogenic therapies for men with prostate cancer.

Target/mechanism	Agent	Phase	Treatment arm(s)	Primary endpoint	Identifier [Ref.]
VEGF ligand (antibodies)	Bevacizumab	II	Single-arm trial: bevacizumab (10 mg/kg IV every 2 weeks) plus temsirolimus (25 mg IV every 1 week) [mCRPC, post-docetaxel]	Objective response rate	NCT01083368 [74]
		II	Randomized trial: androgen deprivation therapy plus bevacizumab (15 mg/kg IV every 3 weeks) versus androgen deprivation therapy alone [biochemically-recurrent prostate cancer]	PSA recurrence-free survival	NCT00776594 [75]
VEGF receptor (TKIs)	Aflibercept (VEGF trap)	III	Randomized trial: aflibercept (6 mg/kg IV) plus docetaxel (75 mg/m ² IV) every 3 weeks versus placebo IV plus docetaxel (75 mg/m ² IV) every 3 weeks [mCRPC, pre-docetaxel]	Overall survival	NCT00519285 [20]
		II	Single-arm trial: sunitinib (37.5 mg orally daily) plus docetaxel (75 mg/m ² IV) every 3 weeks [mCRPC, pre-docetaxel]	30% PSA decline	NCT00879619 [76]
	Sunitinib	II	Single-arm trial: sunitinib (37.5 mg orally daily) plus docetaxel (70 mg/m ² IV every 3 weeks), followed by 66 Gy external-beam radiation [biochemically-recurrent prostate cancer after prostatectomy]	Progression-free survival	NCT00734851 [77]
		II	Single-arm trial: sorafenib (400 mg orally twice daily) [mCRPC, post-docetaxel]	Overall response rate	NCT00414388 [78]
	Cediranib	II	Single-arm trial: sorafenib (400 mg orally twice daily) plus docetaxel (75 mg/m ² IV every 3 weeks) [mCRPC, pre-docetaxel]	50% PSA decline	NCT00589420 [79]
		II	Randomized trial: cediranib (20 mg orally daily) plus docetaxel (75 mg/m ² IV every 3 weeks) versus docetaxel 75 mg/m ² IV every 3 weeks [mCRPC, pre-docetaxel]	Progression-free survival	NCT00527124 [80]
PDGF receptor- β (immunomodulatory drugs)	Cabozantinib	II	Randomized trial: cediranib (20 mg orally daily) plus dasatinib (100 mg orally daily) versus cediranib (20 mg orally daily) [mCRPC, post-docetaxel]	Progression-free survival	NCT01260688 [32]
		II	Single-arm trial: cabozantinib (60 mg orally daily) [mCRPC with bone metastases, pre-docetaxel]	Progression-free survival	NCT01428219 [81]
	Thalidomide	III	Randomized trial: cabozantinib (60 mg orally daily) plus IV placebo every 3 weeks versus mitoxantrone (12 mg/m ² IV every 3 weeks) plus oral placebo daily [mCRPC with bone pain, post-docetaxel and post-abiraterone/MDV3100]	Pain improvement	Pending activation
		II	Single-arm trial: thalidomide (200 mg orally daily) plus liposomal doxorubicin (40 mg/m ² IV every 4 weeks) [mCRPC, post-docetaxel]	Objective response rate	NCT00307294 [82]
	Lenalidomide	II	Single-arm trial: lenalidomide (25 mg orally daily) plus bevacizumab (15 mg/kg IV every 3 weeks) plus docetaxel (75 mg/m ² IV every 3 weeks) [mCRPC, pre-docetaxel]	Overall survival	NCT00942578 [83]
		II	Randomized trial: lenalidomide (25 mg orally daily) versus lenalidomide (5 mg orally daily) versus placebo (orally daily) [biochemically-recurrent prostate cancer]	Progression-free survival	Pending activation

Target/mechanism	Agent	Phase	Treatment arm(s)	Primary endpoint	Identifier [Ref.]
S100A9 protein	Tasquinimod	III	Randomized trial: tasquinimod (1 mg orally daily) versus oral placebo daily [mCRPC, pre-docetaxel]	Progression-free survival	NCT01234311 [64]
Other (cholesterol trafficking and Hedgehog pathway)	Itraconazole	II	Single-arm trial: itraconazole (600 mg orally daily) [mCRPC, post-docetaxel]	30% PSA decline	NCT01450683 [72]

IV; Intravenous; mCRPC: Metastatic castration-resistant prostate cancer; PDGF: Platelet-derived growth factor; PSA: Prostate-specific antigen; TKI: Tyrosine kinase inhibitor.