Anti-angiogenic therapy for prostate cancer: rationale and ongoing trials

Prostate cancer is the most prevalent malignancy among men in the USA with an estimated incidence of 217,730 and the prostate cancer-related death of 32,050 in 2010 [1]. Early-stage prostate cancer may be curable with the prostate cancer-specific survival well over 90% at 15 years in some subgroups [2]. In contrast, the outlook for metastatic prostate cancer is less promising. Androgen-deprivation therapy became the mainstay of the treatment of metastatic prostate cancer after Huggins and Hodges demonstrated its clinical benefit in 1941 [3]. However, most men will progress on androgen-deprivation therapy and develop castration-resistant prostate cancer (CRPC) [4–6]. Until recently, once CRPC developed no single agent or combination of agents improved survival. The US FDA approved mitoxantrone in combination with prednisone in 1996 after palliative responses and the duration of palliation was significantly better than with prednisone alone, although the combination offered no survival advantage [7]. It was not until 2004 that two large randomized clinical trials showed a survival advantage of docetaxel-based chemotherapy over mitoxantrone in patients with metastatic CRPC [8,9]. However, the survival benefits from docetaxel as well as other agents, such as cabazitaxel, sipuleucel-T and abiraterone, which have since been approved by the FDA, are quite modest, hence targeting angiogenesis remains a viable option in this patient population [10–12].

The relevance of tumor angiogenesis

The idea behind inhibition of tumor angiogenic pathways as a treatment strategy stems from the observation that the formation of new blood vessels is required to sustain growth in solid tumors. Ide et al. described the observation of intense neovascularization around a growing tumor in 1939 [13]. In 1971, Folkman suggested that inhibiting angiogenesis may stop tumor growth and metastasis [14]. The relevance of anti-angiogenic therapy was further buttressed by the subsequent isolation of pro-angiogenic agents, such as bFGF, PDGFR, VEGF, endothelins and angiopoietins [15–17].
The VEGF cascade is the most studied among the various pro-angiogenic signaling pathways. At least seven members of the VEGF family of signaling proteins have been described and they include VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F and PIGF [18]. These ligands stimulate cellular response by binding to three different VEGF receptor tyrosine kinases (VEGFR-1, VEGFR-2 and VEGFR-3) on cell surfaces. VEGF-A is the most important member of the VEGF family. It binds to VEGFR-1/Flt-1 and VEGFR-2/KDR/flk-1. VEGFR-1 is expressed on vascular endothelial cells, its role is not well defined, but it seems to modulate VEGFR-2 signaling [19]. VEGFR-2 is expressed on vascular and lymphatic endothelial cells and it appears to modulate almost all of the cellular responses from VEGF binding [20,21]. These functions include proliferation, migration, survival and permeability of endothelial cells.

Endothelin-1 is an amino acid that is involved in vasoconstriction and has been implicated in angiogenesis. Levels of endothelin-1 were found to be elevated in human breast, colorectal, pancreatic, hepatocellular and prostate cancers [22–26]. Endothelin-1 binds to endothelin A and B receptor, although the proliferative and migratory effect on endothelial cells seems to be mediated via the endothelin-B receptor [27].

The angiopoietin–Tie system is a ligand–receptor structure that controls endothelial cell survival and maturation. Angiopoietin-1 is a 498 amino acid polypeptide involved in pericyte recruitment and maintenance of vessel integrity [28]. In the presence of VEGF, angiopoietin-2, a 496 amino acid polypeptide, mediates angiogenesis [29]. If the binding of angiopoietin-1 or angiopoietin-2 leads to homodimerization of the Tie-2 receptors, angiogenesis is induced. However, if there is heterodimerization of Tie-2 with Tie-1, there would be no activation of the Tie-2 receptor, leading to blood vessel quiescence. The expression of angiopoietin-2 has been shown to correlate with histologic grade, vascular density, metastasis and cancer-specific survival in prostate adenocarcinoma [30]. Another potential pathway involved in tumor angiogenesis is the SDF-1–CXCR4 axis, which may be involved in bone metastases [31,32].

**Angiogenesis in prostate cancer**

Angiogenesis has been shown to play an important role in prostate cancer progression in several preclinical models. In most of these studies, surrogate markers of angiogenesis have been shown to correlate with metastasis, Gleason score and prognosis. VEGF expression by immunohistochemistry was found to be significantly higher in prostate cancer cell lines than in normal or benign hyperplastic prostate tissue [33]. Plasma levels of VEGF were shown to be higher in patients with metastatic prostate cancer than those with localized disease [34]. HIF, a transcription factor that plays a critical role in VEGF expression, was noted to be differentially expressed in prostate cancer tissue than in normal prostate tissue [35]. Other pro-angiogenic proteins that may contribute to prostate cancer progression have also been shown to be differentially expressed in prostate cancer. Serum bFGF was significantly higher in men with prostate cancer than their controls without prostate cancer [36]. Endoglin (CD105) is a transmembrane receptor that re-routes TGF-β signaling via a stimulatory pathway leading to endothelial cell proliferation and migration [37]. It is highly expressed on prostate cancer endothelial cells and it is significantly associated with Gleason score, local tumor stage and metastasis [38]. Borre et al. showed that prostate cancer microvessel density at diagnosis was significantly associated with tumor grade and disease-specific survival [39,40]. Other investigators have also demonstrated that microvesSEL density is associated with extraprostatic disease, including bone metastasis [41,42].

The association between these surrogate markers of angiogenesis and adverse tumor features provides the relevance for targeting angiogenesis. The ability of anti-angiogenic agents to inhibit tumor growth in preclinical models further supports the importance of anti-angiogenic therapy [43].

**Anti-angiogenic agents & their targets**

- **PSMA**

PSMA is a transmembrane glycoprotein with an unclear role in malignancy. It is expressed in prostate epithelial cells, but higher expression has been shown in advanced prostate cancer when compared with benign prostatic epithelium [44]. The preferential expression of PSMA on tumor-associated neovasculature and the lack of its expression on normal vascular endothelium [45] makes PSMA a possible target for anti-angiogenic therapy. Unlike PSA and prostatic acid phosphatase, PSMA is a cell surface membrane protein that is not secreted and this characteristic makes it a potential target for therapy with monoclonal antibodies [46,47]. Although the role of PSMA in tumor angiogenesis is not well established, in mouse models it seems to mediate endothelial cell invasion through the extracellular matrix barrier, by modulating laminin-specific integrin signal transduction and p21-activated kinase 1 activity [48]. The human recombinant monoclonal antibody, J591 (MLN591; Millennium Pharmaceuticals, Cambridge, MA, USA), recognizes the extracellular domain of PSMA, and it was developed to induce antibody-dependent cytotoxicity. Radiolabeled forms of J591 were cytotoxic to PSMA-expressing human prostate cancer in preclinical models.
J591 was given with IL-2 in a Phase II clinical trial that enrolled 17 patients with recurrent prostate cancer. The combination was well tolerated but there were no PSA declines of >50% \[51\]. The use of 177 lutetium-labeled J591 in 35 patients with CRPC resulted in ≥50% PSA decline in four of the patients with acceptable toxicities \[52\]. Yttrium-90-labeled J591 also showed some activities in CRPC with acceptable toxicities in a Phase I trial \[53\]. Several Phase II clinical trials using J591-based combination therapies in prostate cancer are currently ongoing (Table 1).

### Endoglin

TRC105 is a human chimeric monoclonal antibody that binds to CD105 (endoglin), an essential target for tumor angiogenesis and growth. In a multi-institutional Phase I dose-finding study, 33 patients with advanced refractory malignancies received TRC105 at doses between 0.01 and 1 mg/kg. At a TRC105 dose of 0.1 mg/kg, one patient experienced grade 4 gastric ulcer bleeding and two patients experienced grade 3 infusion reaction \[54\]. In another Phase I study that had enrolled eight out of the planned 30 patients with metastatic CRPC, TRC105 was given at doses of 1, 3 or 10 mg in three different cohorts. Dose-limiting toxicity was not observed and one patient in cohort 3 had a 51% decline in PSA level \[55\].

### VEGF

Bevacizumab (Avastin®; Genentech, Inc, San Francisco, CA, USA) is a recombinant humanized IgG1 monoclonal antibody that binds to soluble VEGF-A, thus preventing the binding of the ligand to VEGFR. Early preclinical studies demonstrated the ability of VEGF inhibition to arrest tumor growth in human prostate cancer cell lines \[56\]. However, single-agent bevacizumab administered to 15 patients with metastatic CRPC in a Phase II trial did not produce significant objective tumor or PSA responses \[57\]. The combination of VEGF inhibition with conventional cytotoxic chemotherapy led to some promising results in the CALGB 90006 trial. The CALGB 90006 was a Phase II trial of bevacizumab 15 mg/kg given on day 2, docetaxel 70 mg/m² given on day 2 and estramustine 280 mg thrice-daily on days 1–5 of every 21 days. In total, 79 patients with metastatic CRPC were enrolled, of which 77 patients were evaluable. A ≥50% decline in PSA level was observed in 75% of the patients and 59% (23/39) of the patients with measurable disease achieved partial response. The median progression-free survival (PFS) and overall survival (OS) were 8 months and 24 months, respectively \[58\]. In contrast, the combination of docetaxel and bevacizumab did not provide significant OS benefit over docetaxel alone in the Phase III CALGB 90401 trial despite a significant improvement in PFS. CALGB 90401 randomized 1050 chemotherapy-naive patients with metastatic CRPC to receive docetaxel 75 mg/m² every 21 days and prednisone 5 mg twice-daily with either bevacizumab 15 mg/kg every 21 days or placebo \[59\]. The median PFS on the bevacizumab arm was 9.9 months (95% CI: 9.1–10.6) versus 7.5 months (95% CI: 6.7–8.0) in the placebo arm (hazard ratio [HR]: 0.77; 95% CI: 0.68–0.88). The improvement in PFS did not translate to OS benefit, which was 22.6 months (95% CI: 21.1–24.5) versus 21.5 (95% CI: 20.0–30.0) in the bevacizumab and placebo arms, respectively (HR: 0.91; 95% CI: 0.78–1.05). In a Phase II trial, 20 docetaxel-pretreated patients with metastatic CRPC were treated with bevacizumab (10 mg/kg) and docetaxel (60 mg/m²) every 3 weeks. In total, 11 (55%) of the patients had >50% decline in their PSA levels; four of whom were nonresponsive to docetaxel alone previously. Of the eight patients with measurable disease, three (37.5%) had partial responses \[60\].

The combination of bevacizumab and immunotherapy has been explored and the results are promising. Preclinical models suggested that dendritic cell function may be inhibited by VEGF in the tumor

| Table 1. Selected active clinical trials of agents targeting PSMA and endoglin. |
|---------------------------------|------------------|-----------------|-----------------|------------------|
| Trial number | Phase | Regimen | Targets | Primary outcome |
| NCT00916123 | I | 177Lu-J591 mAb + docetaxel + prednisone in mCRPC | PSMA | MTD |
| NCT00195039 | II | 177Lu-J591 mAb in mCRPC | PSMA | PSA and tumor response |
| NCT00859781 | II | 177Lu-J591 or placebo + ketoconazole in PSA relapse (randomized) | PSMA | Tumor response |
| NCT01090765 | I and II | TRC105 in mCRPC | CD105 | MTD and PFS |

Details of trials can be found at \[201\].

*Lu: Lutetium; mAb: Monoclonal antibody; mCRPC: Metastatic castration-resistant prostate cancer; MTD: Maximum tolerated dose; PFS: Progression-free survival.*
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microenvironment and the administration of anti-VEGF antibody may terminate the inhibitory effect. Based on these findings, Rini et al. combined sipuleucel-T (Provenge®; Dendreon, Seattle, WA, USA), a dendritic cell-based therapeutic cancer vaccine, with bevacizumab in a Phase II trial. In total, 22 patients with biochemical-recurrent nonmetastatic prostate cancer were treated with the combination. The results showed a significant increase in the PSA doubling time after treatment, and all patients demonstrated an induction of immune response, suggesting that there could be a potential synergistic or immunologic effect of the combination [61].

VEGFR-Trap (Affibercept®; Sanofi-Aventis, Paris, France; and Regeneron, Tarrytown, NY, USA) is a humanized recombinant decoy protein created by fusing domain 2 of VEGFR-1 and domain 3 of VEGFR-2 to the Fc domain of IgG1 [62]. It was designed to bind VEGF-A, VEGF-B and PIGF, thereby inhibiting angiogenesis [63]. VEGFR-Trap has shown some activity in several tumor types in multiple Phase II trials [64-66]. A multicenter, double-blind, placebo-controlled Phase III trial of VEGFR-Trap in metastatic CRPC recently completed patient accrual and the results are being awaited (NCT00519285) [201].

VEGFR

Several agents that target either the extracellular or the intracellular domains of VEGFR are currently at different stages of development. A recently synthesized pyrrolo[3,2-d]pyrimidine derivative, 20d, with potent inhibition of VEGFR-2 resulted in growth arrest of the DU145 human prostate cancer cell line in a mouse model [67]. IMC-1121, a monoclonal antibody to VEGF-R2, that showed tolerability in a Phase I clinical trial of advanced malignancies [68] is currently being evaluated in a Phase II trial involving patients with metastatic CRPC after progression on docetaxel-based chemotherapy (NCI00683475) [201].

Cediranib (Recentin®; AstraZeneca, Wilmington, DE, USA) is an orally active indole-ether quinazoline compound that inhibits VEGFR-1 and VEGFR-2 [69]. In a Phase II trial of cediranib in patients with postdocetaxel castration-resistant prostate cancer, partial tumor response was observed in six (18%) out of 34 patients with measurable disease. Some patients with tumor response had an increase in the level of PSA indicating that serum PSA level might not be ideal for assessing disease response with cediranib. The most common grade 3 toxicities were fatigue, lymphopenia, hypotenemia and muscle weakness [70]. Cediranib is currently being investigated with dasatinib (NCT01260688) and with docetaxel (NCT00527124) in two ongoing Phase II clinical trials [201].

Sunitinib (Sutent®; Pfizer, NY, USA) is an orally active small molecule tyrosine kinase inhibitor that targets VEGF-1, VEGF-2, PDGFR, c-KIT, FLT3 and RET kinases [71]. The antitumor activity of sunitinib in CRPC has been investigated in both chemotherapy-naive and post-chemotherapy settings. In a Phase II study, Dror Michaelson et al. treated 17 men with chemotherapy-naive CRPC and 17 men with docetaxel-resistant CRPC with sunitinib 50 mg daily for 4 weeks of each 6-week cycle. One man in each group had PSA decline of ≥50%. Changes in PSA did not correlate with radiographic changes because some men with radiographic improvement had elevations in their PSA levels [72]. In another Phase II study, Sonpavde et al. reported a PSA decline of ≥50% in 12.1% of 36 men treated with sunitinib after their metastatic CRPC progressed following docetaxel-based chemotherapy. The median PFS for the cohort was 19.4 weeks and a significant proportion of the men (52.8%) had to discontinue the drug due to toxicities [73]. A Phase III study that randomized men with post-docetaxel metastatic CRPC to prednisone with or without sunitinib was terminated prematurely in September 2010 due to futility (NCT00676650) [201].

Sorafenib (Nexava®, Bayer HealthCare and Onyx Pharmaceuticals, Emeryville, CA, USA) is a multi-tyrosine kinase inhibitor that targets the Raf kinase, c-KIT, VEGFR-2, VEGFR-3, Flt-3 and PDGFR-β [74]. In total, 28 patients with chemotherapy-naive, progressive CRPC were treated with sorafenib 400 mg daily in a Phase II clinical trial [75]. The median number of treatment cycles was two (range: one to eight). One patient had a PSA decline of ≥50%. There was no tumor response in the 12 patients with measurable disease. The median time to PSA progression was 2.1 months (95% CI: 1.8–6.4) and the median OS was 12.25 months (95% CI: 6.7–16.46). Fatigue (54%), skin rash (50%) and hand and foot syndrome (39%) were most common side effects. A larger Phase II trial that treated 64 patients with chemotherapy-naive metastatic CRPC with sorafenib 400 mg daily reported a PSA decline of ≥50% in 13 (20.3%) patients. Seven (20%) of the 35 patients with measurable disease had partial response. The median time to disease progression was 5.9 months [76]. In total, 24 patients with metastatic CRPC, of whom 21 patients had been treated previously with chemotherapy, were enrolled in the National Cancer Institute Phase II trial of sorafenib given at a dose of 400 mg daily [77]. The primary end point was disease progression defined as radiographic or PSA progression. However, the protocol was amended later to define progression solely on radiographic findings. There was no PSA response in any of the patients and, of the 13 patients with measurable...
disease, one had a partial response. The median PFS was 3.7 months with a median OS of 18 months [77]. Sorafenib is being combined with multiple other agents in ongoing clinical trials (Table 2) [201].

Cabozantinib (XL184) is a small-molecule inhibitor of the VEGFR-2 and MET that has shown some activity in prostate cancer. The result of a randomized Phase II trial of cabozantinib in patients with metastatic CRPC was presented at the American Society of Clinical Oncology 2011 annual meeting. Patients were enrolled to receive cabozantinib 100 mg daily for a 12-week period in the lead-in phase. Subsequently, those with partial response continued open-label cabozantinib, those with stable disease were randomized to cabozantinib or placebo and those with disease progression discontinued the drug. Of the accrued 168 patients, 78% of the 100 patients that were evaluable for the lead in-stage had bone metastasis. Of the 65 patients evaluable by bone scan, 56 (86%) had complete or partial resolution of their bone lesions at 6 weeks. The common grade 3 or 4 adverse events were fatigue and hypertension. Adverse events led to the discontinuation of the drug in 10% of the patients and dose reduction in 51% [78].

SU-5416 (Semaxinib®; Pharmacia, San Francisco, CA, USA) is a competitive inhibitor of VEGFR-2. A randomized Phase II trial was stopped prior to full patient accrual because SU-5416 failed to alter the PSA kinetics or time to progression in patients with chemotherapy-naive CRPC [79]. Further development of SU-5416 has now been stopped by the manufacturer. Vandetanib (Zactima®, AstraZeneca), a tyrosine kinase inhibitor directed against VEGFR, EGFR and RET [80] also failed to show efficacy benefit over placebo in a randomized, placebo-controlled, Phase II trial of docetaxel plus prednisone with vandetanib or placebo in metastatic CRPC [81]. Gefitinib (Iressa®; AstraZeneca) an oral EGFR inhibitor, has shown little or no single-agent activity in CRPC in several Phase II studies [82–84].

 FGFR

The FGFs activate transmembrane tyrosine kinase receptors through interaction with heparan sulfate proteoglycans [85]. FGFs control several cellular processes and they are believed to be involved in tumorigenesis. In prostate cancer, components of the FGF signaling pathway may be abnormally expressed [86]. Inhibition

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**Table 2. Selected active clinical trials of agents targeting VEGFR and other receptor tyrosine kinases.**

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Phase</th>
<th>Regimen</th>
<th>Targets</th>
<th>Trial number</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA response, time to PSA progression and toxicity</td>
<td>II</td>
<td>Bevacizumab in PSA-relapsed CRPC</td>
<td>VEGF</td>
<td>NCT00478413</td>
</tr>
<tr>
<td>Relapse-free survival</td>
<td>II</td>
<td>Bevacizumab with ADT for PSA relapse after local therapy (randomized)</td>
<td>VEGF</td>
<td>NCT00776594</td>
</tr>
<tr>
<td>PFS</td>
<td>II</td>
<td>IMC-1121B or IMC-A12 with mitoxantrone and prednisone in mCRPC (randomized)</td>
<td>VEGFR-2</td>
<td>NCT00683475</td>
</tr>
<tr>
<td>PFS</td>
<td>II</td>
<td>Cediranib with or without dasatinib in docetaxel-resistant mCRPC</td>
<td>VEGFR-1, VEGFR-2</td>
<td>NCT01260688</td>
</tr>
<tr>
<td>PFS</td>
<td>II</td>
<td>Cediranib with docetaxel and prednisone in mCRPC (randomized)</td>
<td>VEGFR-1, VEGFR-2</td>
<td>NCT00527124</td>
</tr>
<tr>
<td>PSA response</td>
<td>II</td>
<td>Sunitinib with docetaxel and prednisone in mCRPC</td>
<td>VEGFR-1, VEGFR-2, PDGFR, c-KIT, FLT3, RET kinases</td>
<td>NCT00879619</td>
</tr>
<tr>
<td>PFS</td>
<td>II</td>
<td>Sunitinib maintenance after first-line chemotherapy in CRPC</td>
<td>VEGFR-1, VEGFR-2, PDGFR, c-KIT, FLT3, RET kinases</td>
<td>NCT00550810</td>
</tr>
<tr>
<td>MTD</td>
<td>I</td>
<td>Sunitinib with ADT and RT in high-risk locally advanced prostate cancer</td>
<td>VEGFR-1, VEGFR-2, PDGFR, c-KIT, FLT3, RET kinases</td>
<td>NCT00631527</td>
</tr>
<tr>
<td>PSA response</td>
<td>II</td>
<td>Sorafenib with docetaxel in mCRPC</td>
<td>VEGFR-2, VEGFR-3, PDGFR-β, c-KIT, FLT3, Raf kinase</td>
<td>NCT00589420</td>
</tr>
<tr>
<td>MTD</td>
<td>I</td>
<td>Sorafenib with imatinib in CRPC after chemotherapy failure</td>
<td>VEGFR-2, VEGFR-3, PDGFR-β, c-KIT, FLT3, Raf kinase</td>
<td>NCT00424385</td>
</tr>
<tr>
<td>PSA response</td>
<td>II</td>
<td>TKI258</td>
<td>VEGFR-1, VEGFR-2, VEGFR-3, FGFRs, KIT Ret, FLT3, TrkA, csf-1</td>
<td>NCT00831792</td>
</tr>
</tbody>
</table>

Details of trials can be found at [201].

ADT: Androgen-deprivation therapy; CRPC: Castration-resistant prostate cancer; mCRPC: Metastatic CRPC; MTD: Maximum tolerated dose; PFS: Progression-free survival; RT: Radiotherapy.
of tumorigenesis by ablation of the Frs2α gene in mouse model is an indication that the FGF signaling pathway could be a potential target in prostate cancer therapy. TK1258 is an orally active receptor tyrosine kinase inhibitor that targets VEGFR, FGFR, FLT-3 and other receptor tyrosine kinases. In a Phase I study of TK1258 in advanced solid malignancies one patient with prostate cancer had stable disease for 5 months [87]. TK1258 is currently being investigated in CRPC in a Phase II trial (NCT00831792) [201].

**Angiopoietin–Tie system**
Among the angiopoietin family of ligands, angiopoietin-1 and -2 are the most understood. Their roles are complimentary in the neovascularization process; angiopoietin-2 promotes endothelial cell proliferation and sprouting angiogenesis, while angiopoietin-1 maintains endothelial cell survival, pericyte coverage and vascular maturation [88]. AMG 386 is a peptibody that inhibits the interaction of angiopoietin-1 and -2 with the Tie2 receptor. In a Phase I study of AMG 386 in combination with chemotherapy in advanced solid tumors one out of three patients with prostate cancer had a partial response [89].

**Immunomodulation**
Thalidomide appears to target angiogenesis by its inhibitory action on the activity of bFGF/FGF2, a peptide that exerts its effect on endothelial cells by interacting with heparan sulfate proteoglycans and tyrosine kinase FGF receptors [90,91]. It has also been shown that thalidomide may have antitumor activities by the inhibition of TNF and modulation of endothelial cell surface adhesion molecules [92,93]. A Phase II study reported ≥50% PSA decline in three (15%) out of 20 men with CRPC treated with thalidomide 100 mg daily for up to 6 months [94]. Another open-label Phase II clinical study randomly assigned 75 chemotherapy-naïve patients with metastatic CRPC to receive either docetaxel 30 mg/m² weekly for three out of 4 weeks with thalidomide 200 mg daily or docetaxel alone at the same dose and schedule [95]. After a median follow-up of 26.4 months, 53% of the patients in the combination arm compared with 37% in the single-agent arm had >50% decline in their PSA from baseline. Among the patients with measurable soft tissue disease, 35% in the combination arm and 27% in the single-agent arm had partial response. The updated OS data was in favor of the combination arm over the single-agent arm (25.9 vs 14.7 months; p = 0.0407) [96]. Prior to the initiation of prophylactic anticoagulation with low molecular weight heparin in the docetaxel/thalidomide arm, 12 patients developed either deep vein thrombosis, transient ischemic attack or stroke, while no thromboembolic events were reported in the docetaxel-alone arm.

Lenalidomide is a 4-aminoglutamide derivative of thalidomide with similar activities but fewer side effects [97,98]. In a recent randomized Phase I/II study, 60 patients with nonmetastatic biochemically relapsed prostate cancer were assigned to either lenalidomide 5 mg daily (n = 26) or 25 mg daily (n = 34) for 3 weeks each month for 6 months or until disease progression or dose-limiting toxicity [99]. A decline of >50% in PSA level was noted in six (18%) men in the 25 mg arm and none of the men in the 5 mg arm of the study. Grade 3 and 4 toxicities were more common in the 25 mg arm (29%) versus the 5 mg arm (12%). A Phase I study of 31 patients with CRPC reported that lenalidomide in combination with docetaxel resulted in >50% decline in PSA in 47% of chemotherapy-naïve patients and 50% of previously treated patients [100]. The efficacy of docetaxel with lenalidomide is being tested against docetaxel alone in the ongoing Phase III Mainsail clinical trial (NCT00988208) (Table 3) [201].

**Dual anti-angiogenic therapy**
A Phase II trial combined two anti-angiogenic agents (bevacizumab and thalidomide) with docetaxel and prednisone in 60 men with metastatic CRPC. Docetaxel 75 mg/m² and bevacizumab 15 mg/kg were both given on day 1 of each 21-day cycle. Thalidomide 200 mg and prednisone 10 mg were given daily. The results showed ≥50% decline in PSA level from baseline in 90% of the patients. The median time to progression was 18.3 months (not PSA based) and the median OS was 28.2 months. All the patients developed grade 3 or 4 neutropenia, 13% developed peripheral neuropathy, and grade 2 osteonecrosis of the jaw was observed in 18.3%. There was one death from myocardial infarction complicated by aortic dissection, two cases of gastrointestinal perforation, three cases of grade 3 or 4 rectal fistula or ulcer, five cases of grade 3 bleeding and four cases of grade 3 or 4 thrombosis [101]. Due to the toxicity profile of the combination, thalidomide is being replaced with lenalidomide in a similar Phase II trial currently ongoing at the National Cancer Institute (NCT00942578) (Table 3).

**Resistance to anti-angiogenic therapy**
Multiple mechanisms may be involved in the development of resistance to anti-angiogenic therapy after an initial tumor response. A tumor may evade an anti-angiogenic pathway by inducing compensatory pro-angiogenic pathways within the tumor, or it may recruit pro-angiogenic elements from the bone marrow. In a preclinical model RIP1-Tag2 mice with pancreatic islet cell carcinoma treated with monoclonal antibody
(DC101) directed against VEGFR showed a transient tumor response followed by tumor progression [102]. The relapsing tumor had higher levels of mRNAs for growth factors than the initial tumor. Although there are currently no standardized biomarkers of tumor response or resistance to anti-angiogenic therapy, Fischer and colleagues synthesized an antibody that targets PIGF, which is elevated in tumors treated with VEGF inhibition [103,104]. Neutralizing PIGF with the antibody led to response in tumors resistant to inhibition of VEGF signaling pathway. Tumors that are primarily refractory to anti-angiogenic therapy may be preferentially expressing multiple pro-angiogenic agents even before anti-angiogenic therapy. This is particularly possible in advanced-stage disease [105,106].

**Future perspective**

Inhibition of angiogenesis continues to be an active area of research in prostate cancer therapy. However, the antitumor activities of most single-agent anti-angiogenic therapies in preclinical models have not translated into tumor response and survival benefit in Phase II and III clinical trials. Data from a recent Phase II study suggested that cabozantinib might have a potential role. The results showed an exceptional bone scan improvement in 86% of the patients at 6 weeks of treatment, and based on this finding the drug manufacturer plans to expand the prostate cancer cohort in the study. It would be fascinating to see whether cabozantinib can improve survival in advanced prostate cancer.

Angiogenic inhibition in combination with conventional chemotherapy that has become a standard in other tumor types is also being investigated in prostate cancer. Although findings from the CALGB 90401 trial were not encouraging, the results from the Mainsail trial are being eagerly awaited. Optimal inhibition of angiogenesis may require dual anti-angiogenic therapy, as reported by Ning et al [101]. Toxicity is a potential limitation of this approach. Consequently, there is a need for further research into the simplest, most effective and least toxic anti-angiogenic agent for the treatment of prostate cancer.

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**Executive summary**

- The current treatment options for metastatic castration-resistant prostate cancer only provides modest survival benefit.
- Angiogenesis appears to play a critical role in the pathophysiology of prostate cancer, hence it may be important for targeted therapy.
- Angiogenic pathways mediated by PSMA, CD105, VEGF, PIGF and bFGF have been the targets of several anti-angiogenic compounds currently at different stages of development.
- Cabozantinib appears to be promising, the final result of its Phase II trial are being awaited.
- Bevacizumab with docetaxel and prednisone failed to impart survival in the CALGB 90401 Phase III study. The efficacy of lenalidomide with docetaxel and prednisone is being investigated in the Mainsail trial.
- Dual anti-angiogenic therapy in combination with conventional chemotherapy may have substantial antitumor activity.
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Anti-angiogenic therapy for prostate cancer: rationale & ongoing trials

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