Chapter 14
Targeting Tumor Angiogenesis

Stefania Staibano and Paolo Antonio Ascierto

Abstract Four decades after the seminal work of Judah Folkman, in 1971, cancer therapies based on the suppression of neo-angiogenesis (Folkman, N Engl J Med 285:1182–1186, 1971) are becoming a reality (Verheul et al., Clin Cancer Res 14(11):3589–3597, 2008).

The shift toward the up-regulation of pro-angiogenic factors secretion from both tumor and stroma, results from the interplay between endothelial cell activation, proliferation, extracellular matrix degradation, migration, canalization. It leads to the generation of a chaotic vascular vessels network in prostate cancer tissue (Ahmed and Bicknell, Method Mol Biol 467:3–24, 2009), which can be detected also by modern imaging techniques based on magnetic resonance, ultrasound, and nuclear imaging through targeting of key angiogenic factors (Russo et al., BJU Int 110(11 Pt C):E794–E808, 2012).

This hopefully will lead to further improvements in prostate cancer diagnosis and staging. Preclinical evidence indicates that angiogenesis inhibitors can improve the efficacy of conventional cytotoxic agents mainly by normalizing tumor blood flow, thus improving drug delivery. Although significant biological activity of most vascular growth factors-interfering agents is demonstrated in preclinical models, single-agent activity is almost universally poor (Aragon-Ching et al., J Oncol 2010:361836, 2010). Due to the redundancy within the signalling pathways that promote angiogenesis, combining anti-angiogenic agents with different

S. Staibano (✉)
Department of Advanced Biomedical Sciences, Pathology Section, Faculty of Medicine and Surgery, University of Naples "Federico II", via S. Pansini, n.5, Naples, Italy
e-mail: staibano@unina.it

P.A. Ascierto
Unit of Melanoma, Cancer Immunotherapy and Innovative Therapy, Department of Melanoma, National Institute of Tumors Fondazione "G. Pascale", Via Mariano Semmola 1, 80131 Naples, Italy
e-mail: paolo.ascierto@gmail.com

S. Staibano (ed.), *Prostate Cancer: Shifting from Morphology to Biology*,
DOI 10.1007/978-94-007-7149-9_14,

mechanisms of action seems likely to significatively potentiate their therapeutic efficacy (Corcoran and Gleave 2012; Ellis and Hicklin, Nat Rev Cancer 8: 579–591, 2008; Verheul et al., Cancer Chemother Pharmacol 60:29–39, 2007).

14.1 Prostate Tumor Microenvironment, Hypoxia and Tumor Neoangiogenesis

Stefania Staibano (✉)

Prostate cancer-associated angiogenesis is a well recognised process (Russo et al. 2012).

Microvessel density (MVD) usually is higher in primary tumors of patients with metastatic disease compared with localised prostate cancers (Weidner et al. 1993; Fregene et al. 1993; Strohmeyer et al. 2000; Gravdal et al. 2009). As well, higher MVD correlates with advanced pathological stage (Lee et al. 2004), increased PSA levels (Lee et al. 2001a, b), higher tumor grade (Park et al. 2007), increased metastatic potential (Aragon-Ching and Dahut 2009; Park et al. 2007), and decreased survival of patients (Park et al. 2007; Lee et al. 2001a, b).

Moreover, tumor blood vessels show multiple structural and functional abnormalities (Russo et al. 2012), increased tortuosity, blind ends and high cellular proliferation rate, leading to dysfunctional and heterogeneous tumor tissue microcirculation, with frequent avascular tumor areas, hypoxia, acidosis, and glucose deprivation (Shannon et al. 2003; Teicher et al. 1990; Vaupel et al. 1989; Airley et al. 2000; Brown 1999; Folkman 1971).

This results in a net efflux of fluid into the interstitial space, devoted of functional lymphatics, so that it distends the extracellular matrix and increases the interstitial pressure (An et al. 1998).

All these features are associated with metastatic risk (Siim et al. 1996; Wang et al. 1992; Peters et al. 2001).

VEGF is a 46-kDa dimeric protein also known as a vascular permeability factor (VPF), and represents the most potent growth factor acting in stimulating cell proliferation, angiogenesis and lymphangiogenesis (Ferrer et al. 1998; Shweiki et al. 1995). VEGF, in prostate cancer progression, is regulated by hypoxia (Shweiki et al. 1992, 1995; Minchenko et al. 1994; Walker et al. 1994), cytokines, and androgens; moreover, several oncogenes, as Ras-, Raf-, and Src, the inactivation of tumor-suppressor genes as p53 and von Hippel – Lindau (Ravi et al. 2000) concur to its modulation.

VEGF immunohistochemical expression is highest in metastatic prostatic cancer tissue, but it does not predict prostate cancer progression (Botelho et al. 2010), nor correlates with VEGF expression and clinical and pathological features of tumors (Shariat et al. 2004).

VEGF acts in a paracrine manner by binding its receptors (VEGF-R1 and VEGF-R2) expressed on the surface of endothelial cells. VEGF binding activates the receptor's tyrosine kinase activity, and via the stimulation of several molecular pathways, as ERK and Akt, leads to vasodilatation, increased vascular permeability, cell proliferation, degradation and invasion of the underlying stroma (Aragon-Ching and Dahut 2009).

However, these vascular growth factors have multiple functions. As an example, prostate cancer cells overexpress also the VEGF receptor (VEGFR), so VEGF and VEGFR reciprocally act in an autocrine manner promoting, besides neo-angiogenesis, prostate cancer cell proliferation and survival (Jackson et al. 2002). In addition, it inhibits tumor cell apoptosis by inducing the expression of the anti-apoptotic protein Bcl-2 (Pidgeon et al. 2001).

Addition of VEGF inhibitors to antiandrogen therapy results in increased oxygen delivery to hypoxic tumors areas and thus further potentiates radiation therapy (Zhu and Kyprianou 2008).

Prostate tumor cells respond to hypoxia with the over-transcription of the hypoxia-inducible factor-1a (HIF-1) (Rang et al. 1999), which in turn overstimulates VEGF production and leads to neo-angiogenesis (Cvetkovic et al. 2001). VEGF production and signaling is partly dependent on mTOR induced expression of HIF-1a (Treins et al. 2002).

HIF-1a is hydroxylated at the proline residue and degraded by interaction with the von Hipple-Lindau protein complex and proteosome machinery (Semenza 2003; Forsythe et al. 1996) in normoxic conditions. In prostate cells, androgens can activate HIF-1 through an autocrine loop, and HIF-1 interacts with AR on PSA gene promoter, thereby activating its expression (Zhong et al. 2008).

Under hypoxic conditions, as in advanced prostate cancer, HIF-1a protein is stabilized and translocated into the nucleus for specific gene expression regulation including VEGF, and regulates intracellular pH, metabolism, cell invasion and autophagy, preventing death of aggressive cancer cells (Pouyssegur et al. 2006).

HIF-1a is then a preferential target for the development of anticancer drugs (Pili and Donehower 2003).

Histone deacetylase (HDAC) inhibitors have shown an anti-angiogenic activity mediated in part by HIF-1a down-regulation in both tumor and endothelial cells, with the consequent down-regulation of VEGF and other HIF-1a regulated angiogenesis-related genes (Qian et al. 2004). Class II HDAC are important modifiers of HIF-1a. Recently, it has been reported that the HDAC inhibitor LBH589 reduced tumor growth and angiogenesis in a preclinical prostate cancer model (Qian et al. 2006a, b).

Prostate cancer cells overexpress also TGF β, which promotes either extracellular matrix production and angiogenesis (Russell et al. 1998), favouring also osteoblastic bone metastases in experimental systems. The increase of TGF β RI is associated with high-grade and higher clinical stage of prostate cancer.

TGFβ RI expression correlates with tumor vascularity, tumor grade, and metastasis (Wikström et al. 2001). On the opposite side, TGF β RIII expression is decreased or lost in most human prostate cancers, where it correlates with advanced tumor stage and high risk of PSA recurrence.

The occurrence of intraepithelial prostate cancer correlates instead with the loss of TGF β RII responsiveness in stromal fibroblasts. Thus, partially blocking TGFβ through angiogenesis inhibitors, e.g. angiostatin and endostatin could potentially reverse the continuous stimulation of tumor angiogenesis (Deryugina and Quigley 2006).

Prostate cancer has the ability to produce MMPs, TGFβ; and cyclooxygenase 2 (COX-2).

Several endogenous inhibitors of angiogenesis have also been described in prostate cancer, namely angiostatin, endostatin, PSA, TSP1, interleukin 8, and interferons.

Overall, the microenvironment of prostate cancer is a critical determinant in cancer genesis (Chung et al. 2005).

14.2 Targeting the Angiogenic Pathways in Castration-resistant Prostate Cancer

Paolo Antonio Ascierto (✉)

Monoclonal antibody Bevacizumab is a recombinant humanized IgG1 monoclonal antibody with high affinity and specificity for all VEGF-A isoforms. Upon binding to soluble VEGF-A, bevacizumab limits ligand binding to EC receptors VEGFR-1 and VEGFR-2, thus blocking pro-angiogenic intracellular signals transduction.

In a phase II study, Reese et al. evaluated bevacizumab at 10 mg/kg every 14 days for 6 cycles in 15 chemotherapy-naïve patients with CRPC. No objective responses were showed.

But there was a PSA decline (less than 50 %) in 27 % of patients. Antibodies to VEGF slow tumor proliferation in prostate cancer xenograft models, especially when combined with chemotherapy (Gross et al. 2009; Antonarakis and Armstrong 2011).

Despite strong preclinical rationale, a phase III randomized study in men with chemotherapy-untreated CRPC (CALGB 90401) failed to show a survival advantage with the anti-VEGF antibody bevacizumab when combined with docetaxel compared with docetaxel used alone (22.6 vs 21.5 months), although significant improvements were seen with respect to PSA responses (70 vs 58 %) and radiographic responses (53 vs 42 %), as well as progression-free survival (9.9 vs 7.5 months) (George et al. 2011).

However, these results do not indicate that antiangiogenic therapies 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 (cardiovascular events, neutropenic complications) in this older population with multiple co-morbidities. To this end,

it was reported that the presence and number of co-morbidities (for example, 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 co-morbidities in the docetaxel-bevacizumab arm (Wu et al. 2005).

Future development of this and other antiangiogenic agents may rely on combinations with other classes of angiogenesis inhibitors or other chemotherapeutic drugs whose toxicities do not overlap, and will require careful patient selection for those men most likely to benefit and not be harmed by this class of agents.

Combinations of bevacizumab with other agents were also evaluated. The phase II trial CALGB 90006 enrolled 79 patients with metastatic CRPC patients who were treated with docetaxel (70 mg/mq every 21 days), bevacizumab (15 mg/kg every 21 days) and estramustine (280 mg on days 1–5 of the 21 day cycle).

Promising results were showed with a median PFS of 8 months and a median OS of 24 months, with a PSA decline (higher than 50 %) in 75 % of patients (epub.theoncologist.com) (Sturge et al. 2011).

In a phase III trial with metastatic CRPC, 1,050 patients were randomized to receive docetaxel (75 mg/mq every 21 days), prednisone (5 mg twice daily) and either bevacizumab (15 mg/kg every 21 days) or placebo.

This study showed, despite an improvement in the secondary endpoints of progression-free survival (PFS), measurable disease response and post-therapy PSA decline, but the combination with bevacizumab was not statistically significant for OS (22.6 vs 21.5 months). Furthermore, there was higher toxicity in the experimental arm (epub.theoncologist.com).

Other combinations of bevacizumab with other drugs (cytotoxin agents and immunotherapy) didn't show results and further studies are needed. Sunitinib is an oral TKI targeted to all three VEGFR isoforms as well as PDGFβ and KIT, currently approved for renal cell carcinoma (Powles et al. 2011) and gastrointestinal stromal tumor. Several phase II studies of sunitinib were conducted in patients with metastatic CRPC, both in chemotherapy-naïve patients and in post-docetaxel setting (epub.theoncologist.com).

Also a multicenter, randomized, double-blind phase III trial comparing sunitinib plus prednisone versus prednisone alone (NCT00676650) in patients with post docetaxel progressive metastatic CRPC was conducted. But This trial has been recently interrupted prematurely since the combination of sunitinib with prednisone didn't improve OS when compared to prednisone alone.

Aflibercept is a recombinant fusion protein of the extracellular domain of human VEGF-R1 and VEGF-R2 and the Fc portion of human IgG. It acts as a 'VEGF trap' or decoy receptor, binding free ligand and preventing it from interacting with and activating membrane-bound receptor. As expected, it potently binds all naturally occurring ligands of VEGF-R1 and VEGF-R2, including VEGF-A, VEGF-B, and placental growth factor, and so may be anticipated to possess greater anti-angiogenic activity than bevacizumab. In phase I trials, the combination of aflibercept and

docetaxel was shown to be safe and well tolerated, and the combination is now under evaluation in a large phase III trial (VENICE study) in patients with mCRPC.51 This study has completed accrual of approximately 1,200 patients, and is expected to report in mid-2012, with overall survival as the primary endpoint (Corcoran and Gleave 2012).

Other immunomodulatory-antiangiogenic agents like Thalidomide have been studied. The best data on thalidomide were in combination with other cytotoxic agents. Weekly docetaxel (30 mg/mq weekly for 3 out every 4 weeks) with or without thalidomide (200 mg/day) has been evaluated in chemotherapy-naïve metastatic CRPC. The combination arm was favored in terms of PSA decline (53 versus 37 % experiencing >50 % decrease in PSA) and PFS (5.9 versus 3.7 months). The most frequent adverse events were fatigue, peripheral neuropathy and constipation. Furthermore the combination arm may increase thromboembolic events and requires prophylactic anticoagulant therapy. Lenalidomide is an analog of thalidomide that has been evaluated in CRPC patients showing lower toxicity than thalidomide and a better antiangiogenic effect (Merino et al. 2011).

A phase I–II trial evaluating efficacy and tolerability of lenalidomide has been conducted and it compared lenalidomide 5 versus 25 mg/day, administered during 6 months, or until progression, in 60 patients, without hormonal therapy, after PSA relapse. Main toxicity was neutropenia, thrombotic events, asthenia and rash, with more grades 3–4 events in the 25 mg dose arm. Despite higher toxicity, PSA decline curve was favourable to patients receiving the 25 mg/day dose. The first results of a phase II trial combining bevacizumab, lenalidomide, docetaxel and prednisone in CRPC patients were presented at ASCO meeting 2011.

Among 24 patients who had completed four or more cycles, 22 patients had a >50 % PSA decline, and 20 patients had >75 % PSA decline, 14 patients, with measurable disease, showed 2 RC, 9 PR and 3 SD (overall response rate of 78.6 %). Therefore this combination seems to be associated with a high response rate with manageable toxicity. A phase III trial comparing different doses of lenalidomide combined with docetaxel-prednisone versus placebo is, however, currently underway (Merino et al. 2011).

Although one might conclude from these studies that antiangiogenic therapies are ineffective in mCRPC, we believe these negative data highlight an important biologic principle in prostate cancer angiogenesis that should inform the design of future trials (Antonarakis and Armstrong 2011). Specifically, the bone marrow microenvironment contains multiple proangiogenic factors in addition to VEGF including PDGF, basic fibroblast growth factor (bFGF), interleukin 8, and other soluble cytokines. This multiplicity of angiogenic pathways creates “redundancy” and the potential for “tumor escape” from antiangiogenic therapies and suggests that blocking multiple pathways simultaneously, rather than VEGF alone, may be necessary to effectively block angiogenesis in mCRPC. In support of this, our experience with clinical trials suggests that blocking PDGF and VEGF simultaneously (with sunitinib) is more potent in eliciting PSA responses in patients with mCRPC than blocking either VEGF alone (with bevacizumab) or PDGF alone (with imatinib) (Chi et al. 2005). Reflecting these data, studies are currently

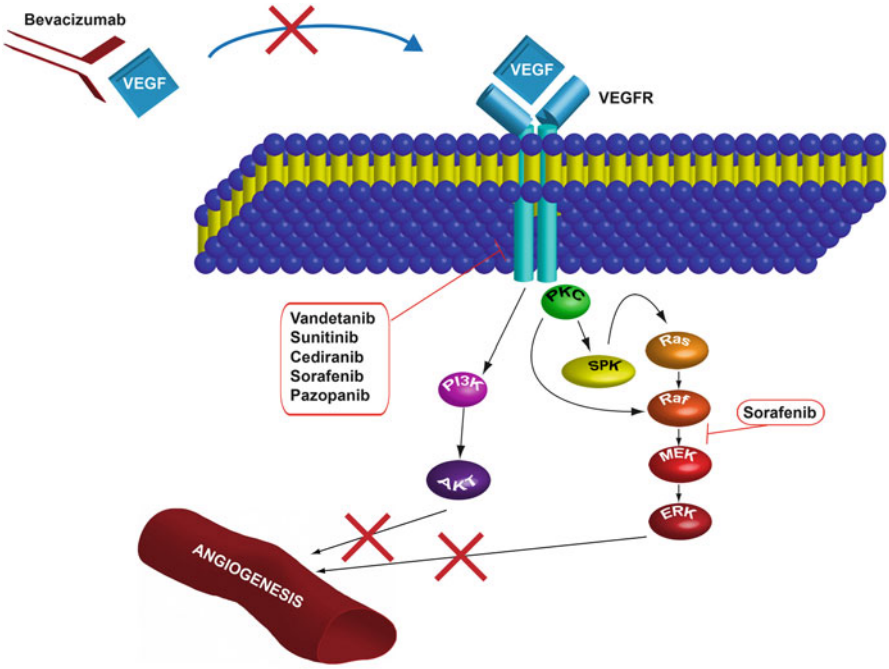

Fig. 14.1 Therapies targeting angiogenic pathway. Vascular endothelial growth factor (VEGF) and its receptors (VEGFR-1, VEGFR-2 and VEGFR-3) provide for new vessel formation and their maintenance. VEGF expression is markedly higher in prostate cancer specimens compared to non-neoplastic prostatic tissue controls and plasma VEGF levels are significantly higher with metastatic versus localized disease. Bevacizumab is a recombinant humanized IgG1 monoclonal antibody with high affinity and specificity for all isoforms of VEGF-A. It binds to soluble VEGF-A limiting ligand binding to EC receptors VEGFR-1 and VEGFR-2 and blocking the transduction of proangiogenic intracellular signals. Sorafenib, sunitinib and Cediranib are multitargeted receptor tyrosine kinase inhibitors (TKI), that exerts their antiangiogenic effect targeting, respectively, RAF kinase, VEGFR-2 and platelet-derived growth factor receptor (PDGFR-β), the three VEGFR isoforms, PDGFβ and KIT, and VEGFR 1 and 2

underway using tyrosine kinase inhibitors that target multiple angiogenic pathways (e.g., TKI258, which potently blocks VEGF, PDGF, and bFGF) (ClinicalTrials.gov identifier: NCT00831792), or alternatively, combine agents that block angiogenesis through different mechanisms (e.g., combining bevacizumab plus lenalidomide). In addition, in a recent phase I/II study combining sunitinib and docetaxel for the treatment of mCRPC in the frontline setting, patients demonstrated reductions in both PSA levels and tumor burden that were more substantial than a historical cohort of patients receiving docetaxel alone (Fig. 14.1) (Sowery et al. 2008).

The observation that both bevacizumab and sunitinib have shown prolongation of progression-free survival without differences in overall survival also raises the possibility that sustained suppression of angiogenesis is required to affect overall survival (Antonarakis and Armstrong 2011; Dayyani et al. 2011). Enhanced

tumor growth following cessation of antiangiogenic therapy has been described, a "rebound" phenomenon that could influence overall survival (Chi et al. 2009). To address these limitations, it may be necessary to continue antiangiogenic therapy beyond standard definitions of disease progression to observe a beneficial impact on overall survival.

There are many question to be answered to optimize antiangiogenic therapy for advanced prostate cancers.

- The role of several angiogenic regulator factors is still poor understood. As an example, we currently know that the prostate-specific membrane antigen (PSMA) expression in tumor-associated neovasculature is necessary for angiogenesis and endothelial cell invasion, but we are unaware of its real role in angiogenesis (Gordon et al. 2008).
- As well, VEGF activation is probably mediated by other still unknown transcription factors such as the Activator protein 1 (AP-1) transcription factor complex (Shih and Claffey 1998).
- Further studies will also address the predictive role of expression of HIF-1 alpha, VEGF, and other angiogenic growth factors in patients treated with radiotherapy alone. These patients, in fact, lack the beneficial effect on tumor vascularization exerted by a neoadjuvant androgen deprivation. Therefore, the angiogenic markers may be even more important in this subgroup of patients (Vergis et al. 2008).

Anyhow, it is a matter of fact that almost all the key regulators of angiogenesis are upregulated in prostate cancer, particularly in the castration-resistant setting, and this undoubtedly has a great relevance for the gain of prostate cancer aggressiveness. This strongly stimulates the search for new reliable marks for effectively targeting prostate cancer angiogenesis.

References

Ahmed Z, Bicknell R (2009) Angiogenic signalling pathways. Methods Mol Biol 467:3–24

Airley RE, Monaghan JE, Stratford IJ (2000) Hypoxia and disease: opportunities for novel diagnostic and therapeutic prodrug strategies. Pharm J 264:666–673

An WG, Kanekal M, Simon MC, Maltepe E, Blagosklonny MV, Neckers LM (1998) Stabilization of wild-type p53 by hypoxiainducible factor-1a. Nature 392:405–408

Antonarakis ES, Armstrong AJ (2011) Emerging therapeutic approaches in the management of metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis 14(3):206–218

Aragon-Ching JB, Dahut WL (2009) VEGF inhibitors and prostate cancer therapy. Curr Mol Pharmacol 2:161–168

Aragon-Ching JB, Madan RA, Dahut WL (2010) Angiogenesis inhibition in prostate cancer: current uses and future promises. J Oncol 2010:361836

Botelho F, Pina F, Lunet N (2010) VEGF and prostate cancer: a systematic review. Eur J Cancer Prev 19:385–392

Brown JM (1999) The hypoxic cell: a target for selective cancer therapy – eighteenth Bruce F. Cain Memorial Award Lecture. Cancer Res 59:5863–5870

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

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

Chung LW, Baseman A, Assikis V, Zhau HE (2005) Molecular insights into prostate cancer progression: the missing link of tumor microenvironment. J Urol 1(73):10–20

Corcoran NM, Gleave ME (2012) Targeted therapy in prostate cancer. Histopathology 60(1): 216–231

Cvetkovic D, Movsas B, Dicker AP, Hanlon AL, Greenberg RE, Chapman JD, Hanks GE, Tricoli JV (2001) Increased hypoxia correlates with increased expression of the angiogenesis marker vascular endothelial growth factor in human prostate cancer. Urology 57(4):821–825

Dayyani F, Gallick GE, Logothetis CJ, Corn PG (2011) Novel therapies for metastatic castrate-resistant prostate cancer. J Natl Cancer Inst 103(22):1665–1675

Deryugina EI, Quigley JP (2006) Matrix metalloproteinases and tumor metastasis. Cancer Metastasis Rev 25:9–34

Ellis LM, Hicklin DJ (2008) VEGF-targeted therapy: mechanisms of antitumour activity. Nat Rev Cancer 8:579–591

Ferrer FA, Miller LJ, Andrawis RI et al (1998) Angiogenesis and prostate cancer: *in vivo* and *in vitro* expression of angiogenesis factors by prostate cancer cells. Urology 51:161–167

Folkman J (1971) Tumour angiogenesis: therapeutic implications. N Engl J Med 285:1182–1186

Forsythe JA, Jiang BH, Iyer NV et al (1996) Activation of vascular endothelial growth factor gene transcription by hypoxia-inducible factor 1. Mol Cell Biol 16:4604–4613

Fregene TA, Khanuja PS, Noto AC et al (1993) Tumor-associated angiogenesis in prostate cancer. Anticancer Res 13:2377–2381

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

Gordon IO, Tretiakova MS, Noffsinger AE, Hart J, Reuter VE, Al-Ahmadie HA (2008) Prostate-specific membrane antigen expression in regeneration and repair. Mod Pathol 12:1421–1427

Gravdal K, Halvorsen OJ, Haukaas SA, Akslen LA (2009) Proliferation of immature tumor vessels is a novel marker of clinical progression in prostate cancer. Cancer Res 69:4708–4715

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

Jackson MW, Roberts JS, Heckford SE et al (2002) A potential autocrine role for vascular endothelial growth factor in prostate cancer. Cancer Res 62:854–859

Lee LF, Guan J, Qiu Y, Kung HJ (2001a) Neuropeptide-induced androgen independence in prostate cancer cells: roles of nonreceptor tyrosine kinases Etk/Bmx, Src, and focal adhesion kinase. Mol Cell Biol 21:8385–8397

Lee SE, Chung WJ, Kwak HB et al (2001b) Tumor necrosis factor-alpha supports the survival of osteoclasts through the activation of Akt and ERK. J Biol Chem 276:49343–49349

Lee LF, Louie MC, Desai SJ et al (2004) Interleukin-8 confers androgenin dependent growth and migration of LNCaP: differential effects of tyrosine kinases Src and FAK. Oncogene 23: 2197–2205

Merino M, Pinto A, González R, Espinosa E (2011) Antiangiogenic agents and endothelin antagonists in advanced castration resistant prostate cancer. Eur J Cancer 47(12):1846–1851

Minchenko A, Bauer T, Salceda S, Caro J (1994) Hypoxic stimulation of vascular endothelial growth factor expression in vitro and in vivo. Lab Invest 71:374–379

Park SI, Shah AN, Zhang J, Gallick GE (2007) Regulation of angiogenesis and vascular permeability by Src family kinases: opportunities for therapeutic treatment of solid tumors. Expert Opin Ther Targets 11:1207–1217

Peters KB, Wang H, Brown JM, Iliakis G (2001) Inhibition of DNA replication by Tirapazamine. Cancer Res 61:5425–5431

Pidgeon GP, Barr MP, Harmey JH, Foley DA, Bouchier-Hayes DJ (2001) Vascular endothelial growth factor (VEGF) up regulates Bcl-2 and inhibits apoptosis in human and murine mammary adenocarcinoma cells. Br J Cancer 85:273–278

Pili R, Donehower RC (2003) Is HIF-1a a valid therapeutic target? J Natl Cancer Inst 95:498–499

Pouyssegur J, Dayan F, Mazure NM (2006) Hypoxia signalling in cancer and approaches to enforce tumour regression. Nature 441:437–443

Powles T, Chowdhury S, Jones R et al (2011) Sunitinib and other targeted therapies for renal cell carcinoma. Br J Cancer 104:741–745

Qian DZ, Wang X, Kachhap SK et al (2004) The histone deacetylase inhibitor NVP-LAQ824 inhibits angiogenesis and has a greater antitumor effect in combination with the vascular endothelial growth factor receptor tyrosine kinase inhibitor PTK787/ZK222584. Cancer Res 64:6626–6634

Qian DZ, Kachhap SK, Collis SJ et al (2006a) Class II histone deacetylases are associated with VHL-independent regulation of hypoxia-inducible factor 1a. Cancer Res 66:8814–8821

Qian DZ, Kato Y, Shabbeer S et al (2006b) Targeting tumor angiogenesis with histone deacetylase inhibitors: the hydroxamic acid derivative LBH589. Clin Cancer Res 12:634–642

Rang HP, Dall MM, Ritter JM (1999) Pharmacology, 4th edn. Churchill Livingstone, Edinburgh, pp 670–677

Ravi R, Mookerjee B, Bhujwalla ZM et al (2000) Regulation of tumor angiogenesis by p53-induced degradation of hypoxia inducible factor 1alpha. Genes Dev 14:34–44

Russell J, Bennett S, Stricker P (1998) Growth factor involvement in progression of prostate cancer. Clin Chem 44:705–723

Russo G, Mischi M, Scheepens W, De la Rosette JJ, Wijkstra H (2012) Angiogenesis in prostate cancer: onset, progression and imaging. BJU Int 110(11 Pt C):E794–E808

Semenza GL (2003) Targeting HIF-1for cancer therapy. Nat Rev Cancer 3:721–732

Shannon AM, Bouchier-Hayes DJ, Condron CM, Toomey D (2003) Tumour hypoxia, chemotherapeutic resistance and hypoxia-related therapies. Cancer Treat Rev 29(4):297–307, Review

Shariat SF, Anwuri VA, Lamb DJ, Shah NV, Wheeler TM, Slawin KM (2004) Association of preoperative plasma levels of vascular endothelial growth factor and soluble vascular cell adhesion molecule – 1 with lymph node status and biochemical progression after radical prostatectomy. J Clin Oncol 22:1655–1663

Shih SC, Claffey KP (1998) Hypoxia-mediated regulation of gene expression in mammalian cells. Int J Exp Pathol 79:347–357

Shweiki D, Itin A, Soffer D, Keshet E (1992) Vascular endothelial growth factor induced by hypoxia may mediate hypoxia initiated angiogenesis. Nature 359:843–845

Shweiki D, Neeman M, Itin A, Keshet E (1995) Induction of vascular endothelial growth factor expression by hypoxia and by glucose deficiency in multicell spheroids: implications for tumour angiogenesis. Proc Natl Acad Sci USA 92:768–772

Siim BG, van Zijl PL, Brown JM (1996) Tirapazamine-induced DNA damage measured using the comet assay correlates with cytotoxicity towards hypoxic tumour cells in vitro. Br J Cancer 73:952–960

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

Strohmeyer D, Rossing C, Strauss F, Bauerfeind A, Kaufmann O, Loening S (2000) Tumor angiogenesis is associated with progression after radical prostatectomy in pT2/pT3 prostate cancer. Prostate 42:26–33

Sturge J, Caley MP, Waxman J (2011) Bone metastasis in prostate cancer: emerging therapeutic strategies. Nat Rev Clin Oncol 8(6):357–368

Teicher BA, Holden SA, Al-Achi A, Herman TS (1990) Classification of antineoplastic treatments by their differential toxicity toward putative oxygenated and hypoxic tumour subpopulation in vivo in the FSaIIC murine fibrosarcoma. Cancer Res 50:3339–3344

Treins C, Giorgetti-Peraldi S, Murdaca J, Semenza GL, Van Obberghen E (2002) Insulin stimulates hypoxia inducible factor 1 through a phosphatidylinositol 3-kinase/target of rapamycin-dependent signaling pathway. J Biol Chem 277:27975–27981

Vaupel P, Kallinowski F, Okunieff P (1989) Blood flow, oxygen and nutrient supply, and metabolic microenvironment of human tumours: a review. Cancer Res 49:6449–6465

Vergis R, Corbishley CM, Norman AR et al (2008) Intrinsic markers of tumour hypoxia and angiogenesis in localised prostate cancer and outcome of radical treatment: a retrospective analysis of two randomised radiotherapy trials and one surgical cohort study. Lancet Oncol 9:342–351

Verheul HM, Qian DZ, Carducci MA, Pili R (2007) Sequence-dependent antitumor effects of differentiation agents in combination with cell cycle-dependent cytotoxic drugs. Cancer Chemother Pharmacol 60:29–39

Verheul HM, Salumbides B, Van Erp K, Hammers H, Qian DZ, Sanni T, Atadja P, Pili R (2008) Combination strategy targeting the hypoxia inducible factor-1 alpha with mammalian target of rapamycin and histone deacetylase inhibitors. Clin Cancer Res 14(11):3589–3597

Walker LJ, Craig RB, Harris AL, Hickson ID (1994) A role for the human DNA-repair enzyme HAP1 in cellular-protection against DNA-damaging agents and hypoxic stress. Nucleic Acids Res 22:4884–4889

Wang J, Biedermann KA, Brown JM (1992) Repair of DNA and chromosome breaks in cells exposed to SR 4233 under hypoxia or to ionizing radiation. Cancer Res 52:4473–4477

Weidner N, Carroll R, Flax J, Blumenfeld W, Folkman J (1993) Tumor angiogenesis correlates with metastasis in invasive prostate carcinoma. Am J Pathol 143:401–409

Wikström P, Damber J, Bergh A (2001) Role of transforming growth factor-beta1 in prostate cancer. Microsc Res Tech 52:411–419

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

Zhong D, Liu X, Khuri FR, Sun SY, Vertino PM, Zhou W (2008) LKB1 is necessary for Akt-mediated phosphorylation of proapoptotic proteins. Cancer Res 68(18):7270–7277

Zhu ML, Kyprianou N (2008) Androgen receptor and growth factor signaling cross-talk in prostate cancer cells. Endocr Relat Cancer 15:841–849