

MET and VEGF: synergistic targets in castration-resistant prostate cancer

Dana T. Aftab · Donald M. McDonald

Received: 26 August 2011 / Accepted: 20 September 2011

Abstract Recent advances in the treatment of prostate cancer have resulted in improved outcomes, including longer survival, but new options are needed for treating patients with castration-resistant disease, particularly in the presence of bone metastasis. Data from preclinical models and clinical biomarker studies indicate that antiangiogenic agents should be a promising treatment for this patient population, and multiple agents in this class have demonstrated activity in early-stage clinical trials. Pivotal trials in prostate cancer with agents targeting vascular endothelial growth factor (VEGF) signalling have resulted in significant improvements in tumour response and progression-free survival. However, overall survival was not significantly improved. Recent preclinical studies suggest that the limited impact on overall survival may result from the development of evasive resistance after inhibition of angiogenesis, possibly through upregulation of MET (hepatocyte growth factor receptor) signalling. MET plays important roles in angiogenesis, tumour cell invasion and bone metastasis, all of which are key factors in castration-resistant prostate cancer. Inhibition of both the MET and VEGF pathways may improve the efficacy of angiogenesis inhibitors in prostate cancer.

Keywords Angiogenesis inhibitors · c-met proteins · Prostate cancer · Neoplasm invasiveness · Metastasis

Introduction

Prostate cancer is the most common non-cutaneous cancer in men. In 2010, an estimated 217,730 new prostate cancer cases were diagnosed in the USA, and more than 32,000 deaths were estimated to occur, making it the second-leading cause of cancer-related death in men [1]. As prostate cancer cells express androgen receptors and are initially androgen-dependent, hormonal-based therapy—also referred to as androgen deprivation therapy—is the initial treatment of choice [2]. While the disease typically responds to this therapy, nearly all patients eventually progress despite castrate levels of androgens (<50 ng/ml); at this stage the disease is known as castration-resistant prostate cancer (CRPC) [2]. Early clinical manifestations of progressive CRPC include bone metastases, rising serum prostate-specific antigen (PSA) levels and pain [3]. Multiple drugs have been approved for CRPC, including the chemotherapeutics docetaxel and cabazitaxel, the immunotherapeutic sipuleucel-T, and the androgen biosynthesis inhibitor abiraterone [4]. While these agents can prolong survival, the prognosis for CRPC remains poor and new therapeutic approaches are needed.

D.T. Aftab (✉)
Exelixis, Inc.
210 East Grand Avenue
South San Francisco, CA 94083-0511, USA
e-mail: daftab@exelixis.com

D.M. McDonald
Comprehensive Cancer Center
Cardiovascular Research Institute and Department of Anatomy
University of California-San Francisco
San Francisco, CA, USA

Antiangiogenic therapy in prostate cancer

Angiogenesis is essential for tumour growth and metastasis [5–7]. Antiangiogenic approaches, most of which rely on

targeting the vascular endothelial growth factor (VEGF) signalling pathway, have emerged as important therapeutic options in treating a range of cancers, including those of the lung, colon, breast and kidney. VEGF-driven angiogenesis also appears to be a promising target in prostate cancer. Expression of VEGF is low in normal prostate tissues [8] but is upregulated in metastatic prostate cancer [8, 9]. In addition, the microvascular density of prostate tumours correlates with disease progression [10, 11], and elevated levels of VEGF in plasma or urine correlate with advanced stage, progression and poor patient outcomes in prostate cancer [9, 12, 13].

Based on these findings, and on promising treatment responses in other tumour types, multiple antiangiogenic agents that target VEGF signalling have been studied in patients with CRPC. Improvement in tumour response and/or progression-free survival was observed with bevacizumab, sorafenib, sunitinib and cediranib in phase 2 trials in CRPC [14–20]. Similar benefits were observed with bevacizumab and sunitinib in phase 3 trials [21, 22]. However, statistically significant improvement in overall survival was not found in the latter pivotal trials.

Similar results were obtained with several antiangiogenic agents in a variety of tumour types other than CRPC, where evidence of initial clinical benefit, such as tumour response and delayed progression, was not accompanied by improved overall survival in pivotal trials [23, 24]. Additionally, while agents that target the VEGF signalling pathway have been clinically important in treating some tumour types, their efficacy in many patients is transient and eventually followed by tumour growth and progression [25–27]. In glioblastoma, relapse in some patients was associated with a concerning increase in tumour invasion and multifocal spread within the brain [28, 29]. These clinical outcomes suggest that the failure to achieve enduring clinical benefit with treatment in some trials may result from the development of resistance to antiangiogenic therapy.

Rationale for targeting MET

Experiments in mice have demonstrated that tumours are capable of developing adaptive or evasive resistance to therapies targeting the VEGF signalling pathway [23, 30, 31]. This response of tumours to therapy is characterised by a more highly invasive and metastatic phenotype, and has been described with a wide variety of agents including the small molecule tyrosine kinase inhibitors (TKIs) sunitinib, sorafenib and cediranib, antibodies that recognise and neutralise VEGF (including bevacizumab), and a VEGFR2-targeting antibody [28–30, 32–35]. One potential mechanism for the development of evasive resistance to VEGF-pathway inhibition is upregulation of MET pathway signalling [36].

MET, the receptor for hepatocyte growth factor (HGF), is a receptor tyrosine kinase that plays important roles in

cell motility, proliferation and survival, and is a key factor in tumour angiogenesis, invasiveness and metastasis [37–39]. Both MET mRNA and protein levels are substantially increased by hypoxia, which can increase cell invasion and migration away from hypoxic regions after treatment with an angiogenesis inhibitor [35, 40, 41].

Expression of HGF is increased in murine tumour models resistant to sunitinib, and systemic administration of HGF can cause resistance to sunitinib in models that are otherwise sensitive to sunitinib [42]. Likewise, combined therapy with sunitinib and a selective inhibitor of MET is significantly more efficacious than therapy with either agent alone in sunitinib-resistant murine tumour models [42]. In addition, TKIs such as cabozantinib (XL184) and foretinib (XL880; GSK1363089), which simultaneously target the MET and VEGF signalling pathways, have a profound impact on tumour vasculature and block the development of tumour invasiveness and metastasis [35, 36]. These results are consistent with a contribution of MET signalling to the development of resistance to VEGF inhibition.

In prostate cancer, growing evidence suggests that MET signalling may play an important role in promoting malignancy, even in the absence of VEGF pathway inhibition. Expression of MET is high in benign prostate tissue (largely in basal cells) and in primary and metastatic prostate carcinomas [43–46]. MET expression is higher in bone metastases than in primary tumours or lymph node metastases [47, 48]. Expression of HGF is greater in prostate carcinoma than in benign prostate tissue [11, 13], and high plasma levels of HGF in men with CRPC correlate with decreased overall survival [49].

Data from preclinical and clinical studies suggest that HGF and MET are regulated by androgen signalling in prostatic cells. HGF expression is low in androgen-sensitive CWR22 xenograft tumours and is significantly upregulated in castration-resistant variants [50]. Similarly, androgen-sensitive prostate cancer cell lines grown in the presence of androgen typically express low or undetectable levels of MET, while CRPC cell lines generally express higher levels [46, 51]. MET expression increases substantially in androgen-sensitive cells after androgen withdrawal *in vitro* or after castration in androgen-sensitive xenograft tumours growing *in vivo* [46, 51, 52]. A similar effect has been described in normal rat prostate tissue after castration [46].

These preclinical findings are consistent with clinical observations that MET expression is significantly greater in tumour samples from patients with CRPC than in specimens from patients who have not yet undergone androgen deprivation therapy [53]. A possible mechanism for this difference is evident in molecular studies showing that the androgen receptor directly represses expression of the gene encoding MET via inhibition of its promoter [51]. Overall, these observations indicate that MET expression is particularly high in prostate cancer bone metastases and that increased MET signalling may reflect the emergence of castration-resistant disease.

Table 1 Key trials examining MET inhibition in CRPC

Study	Tumour type	Endpoints	Results	ClinicalTrials.gov identifier/reference
Tivantinib, phase 1	Advanced solid tumours (N=51); CRPC cohort (n=13)	Safety PK/PD assessments Preliminary antitumour activity	Observed decreases in phosphorylated and total MET levels Declines in CTCs and circulating endothelial cells No tumour responses observed	NCT00612209, Yap et al (2011) [69]
Tivantinib, phase 1	Advanced solid tumours	Safety PK/PD assessments Preliminary antitumour activity	Partial response observed in one CRPC patient	NCT00302172, Mekhail et al (2009) [70]
Cabozantinib, phase 2	Advanced solid tumours (N=490); CRPC cohort (n=171)	ORR, PFS Safety PK/PD assessment	In the CRPC cohort, interim results reported significant disease control rates (partial response+stable disease) Reduction or stabilisation of metastatic bone lesions was observed in nearly all evaluable patients	NCT00940225, Hussain et al (2011) [71]
Cabozantinib, phase 1	CRPC	Changes in bone scans, bone biomarkers, and CTCs	Trial is currently recruiting patients	NCT01347788
Rilotumumab+ mitoxantrone+ prednisone, phase 1b/2	CRPC	OS, PFS Safety PK/PD assessment PSA response rate	Trial is ongoing, but no longer recruiting patients	NCT00770848

ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetic; PD, pharmacodynamic; OS, overall survival

Roles for MET and VEGF signalling in bone metastases

The primary cause of morbidity and mortality in patients with CRPC is metastasis to bone, which occurs in about 90% of cases [3, 54]. Bone metastasis is a complex process involving interactions between the cancer cells and components of the bone microenvironment including osteoblasts, osteoclasts and endothelial cells [54]. Bone metastases cause local disruption of normal bone remodelling, with lesions generally exhibiting a propensity for either osteoblastic (bone-forming) or osteolytic (bone-resorbing) activity. Although most CRPC patients with bone metastases have features of both types of lesions, prostate cancer bone metastases are generally characterised as predominantly osteoblastic, with abnormal deposition of unstructured bone accompanied by increased skeletal fractures, spinal cord compression and severe bone pain [54, 55].

Osteoblastic lesions are typically visualised in CRPC patients by bone scan, which detects rapid incorporation of ^{99m}Tc-labelled methylene-diphosphonate (^{99m}Tc-MDP) radiotracer into newly forming or remodelling bone. Increased levels of bone-specific serum alkaline phosphatase, a marker for osteoblast activity, are often observed in CRPC patients with bone metastases and are associated with shorter overall survival [55].

MET signalling can influence osteoblast and osteoclast function. Strong immunohistochemical staining of MET has been observed in osteoblasts in developing bone [56], while both HGF and MET are expressed by osteoblasts and osteoclasts *in vitro* and regulate cellular responses such as proliferation, migration and differentiation [57–60]. Secretion of HGF by osteoblasts has been proposed as a key factor in osteoblast/osteoclast coupling [58] and is thought to promote the development of bone metastases by tumour cells that express MET [61].

Like MET, the VEGF signalling pathway is strongly implicated in bone formation and remodelling. Both osteoblasts and osteoclasts express VEGF and VEGF receptors, which appear to be involved in autocrine and/or paracrine feedback mechanisms regulating cell proliferation, migration, differentiation and survival [62–66]. Experiments using genetically modified mice have shown that angiogenesis and VEGF signalling in osteoblasts are both important in bone development and repair [67, 68].

Clinical studies with inhibitors of MET signalling in CRPC

Based on the preclinical and clinical findings described above, in the treatment of CRPC there is a clear rationale

for inhibition of the MET signalling pathway, either alone or with inhibition of the VEGF pathway. However, very few MET-targeted agents have been studied in this setting (Table 1). A recently completed phase 1 clinical trial studied the safety and tolerability of the selective MET inhibitor tivantinib (ARQ 197) in patients with solid tumours, including 13 patients with CRPC [69]. Phosphorylated and total MET protein in tumour biopsies and number of circulating tumour cells (CTCs) were reduced in some patients after tivantinib treatment. However, objective RECIST tumour responses or PSA responses were not found in this trial and no changes in bone lesions were reported. In a separate phase 1 trial with tivantinib, a partial response was observed in one CRPC patient [70].

Interim results from a phase 2 randomised discontinuation trial of the MET/VEGFR inhibitor cabozantinib in patients with CRPC showed encouraging clinical activity [71]. Regression of soft tissue/visceral lesions was found in 74% of patients and 10 patients met RECIST criteria for a partial response. A subset of patients with stable disease as their best response after the initial 12 weeks of treatment was randomised to receive either cabozantinib or placebo. The cabozantinib-treated group had significant improvement in progression-free survival. Despite substantial activity against soft tissue/visceral lesions, consistent effects on PSA were not observed and PSA was increased in some patients who had signs of clinical benefit [72].

The most intriguing findings in this trial came from the ⁹⁹Tc-MDP bone scans of patients with bone metastases. Complete or partial resolution of lesions visible in bone scans was found in 82% of patients treated with cabozantinib; this improvement was often accompanied by pain relief and reduction in narcotics usage. Reductions in blood-based markers of osteoblast and osteoclast activities were also observed, consistent with diminished activation of these cells in patients with bone lesions. Whether these effects will ultimately translate into improved overall survival will need to be assessed in future clinical trials. Based on the high incidence of improvement in patients with bone lesions, a subsequent phase 1 study was initiated in patients with CRPC to determine the tolerability and activity of lower starting doses of cabozantinib (Table 1).

An ongoing phase 1b/2 trial is evaluating the safety and efficacy of rilotumumab (AMG 102), a monoclonal antibody that blocks the action of HGF, in combination with mitoxantrone and prednisone in patients with previously treated CRPC [73]. Results have not yet been reported for this study; however, in April 2011 the sponsor announced that development of rilotumumab would be discontinued [74].

Beyond PSA: assessing treatment response to antiangiogenic TKIs in CRPC

Many trials evaluating antiangiogenic agents in prostate cancer have used PSA measurements to assess disease

response and progression. Serum PSA is easily and reproducibly measured, and decreased PSA in prostate cancer patients correlates with better overall survival during treatment with androgen deprivation and chemotherapy [75–77]. However, conflicting or confounding changes in serum PSA have been found after treatment of CRPC with antiangiogenic TKIs (Table 2). Few patients in trials with cediranib, sorafenib, sunitinib and cabozantinib had declines in PSA despite reductions in pain and lymph node, lung, liver and/or bone lesions [16–20, 71, 72, 78, 79]. In some patients with objective tumour regression and reduced pain, PSA levels increased substantially during treatment and then decreased after discontinuation of treatment [16, 20, 79].

In vitro experiments have shown that PSA secretion from prostate cancer cells can increase during incubation with sorafenib [16] and PSA expression in prostate cancer cells can decrease in the presence of osteoblasts [80]. These results suggest that during treatment of CRPC patients with angiogenesis inhibitors, changes in serum PSA may reflect a pharmacodynamic effect of tyrosine kinase inhibition in tumour cells or changes in osteoblast–tumour cell interactions in bone lesions, rather than changes in tumour growth.

In light of these and other observations, the Prostate Cancer Clinical Trials Working Group has emphasised the importance of radiographic or symptomatic progression over PSA progression in trials of antiangiogenic agents, and recommended against discontinuation of therapy solely on the basis of serum PSA changes [3]. These recommendations indicate the need to develop and validate criteria other than PSA progression for assessing treatment effects.

As bone is the most common site of metastasis in prostate cancer, evaluating treatment effects on bone lesions has potential as a useful measure of the therapeutic efficacy of antiangiogenic agents. Changes in bone scan measurements may be more predictive of survival than changes in PSA levels [81, 82]. However, changes in bone metastases are typically difficult to measure objectively and reproducibly by bone scan [83, 84]. New techniques are being developed for computer-assisted detection and assessment of bone lesions that would greatly improve their utility as a standardised measure of treatment effects [85, 86].

CTCs are another promising measure of angiogenesis inhibitor effects in prostate cancer. CTCs have been shown to have prognostic value in CRPC [87, 88]. Lower CTC counts correlate with better overall survival for patients treated with cytotoxic chemotherapy or targeted therapies [89–92]. However, additional clinical trials are needed to validate the use of CTCs as a surrogate endpoint and more robust technologies are needed to improve the detection of CTCs [93].

Conclusions

Ongoing clinical trials of inhibitors of VEGF signalling in CRPC have shown promising results, but thus far no over-

Table 2 PSA and clinical results with antiangiogenic TKIs in CRPC

Study	PSA results	Clinical results	Reference
Cediranib, phase 1 CRPC (N=26)	No PSA declines $\geq 50\%$ during protocol therapy 4 patients with PSA reductions within 30 days after study drug discontinuation, 3 of whom had seen PSA rises while on study therapy Post-therapy PSA declines lasted >17 months in 2 patients despite PSA increases while on therapy	28.6% of patients with best response of SD by RECIST 1 patient with resolution of retroperitoneal adenopathy; exhibited 93% PSA decline after study drug discontinuation	Ryan et al (2007) [20]
Cediranib, phase 2 CRPC (N=53)	PSA levels increased dramatically in some patients with tumour responses	55.9% of patients with evaluable disease had tumour shrinkage 17.6% of patients with best response of PR by RECIST Decreases in metastases in lymph nodes, lung, liver and bone	Adelberg et al (2010) [17]
Cabozantinib, phase 2 with mCRPC cohort (N=171)	PSA changes not correlated with other efficacy parameters	68% disease control rate (PR+SD) at week 12 74% of patients had measurable disease regression Pain improvement in 67% of patients with pain at baseline 82% of patients had complete or partial resolution of lesions on bone scan	Smith et al (2011) [72] Hussain et al (2011) [71]
Sorafenib, phase 2 mCRPC in two stages (n=22 and n=24)	No PSA response in either stage; in stage 1, 61.9% of patients progressed only by PSA criteria in the absence of clinical and radiographic progression	In stage 1, 2 patients showed regression in bone lesions despite meeting PSA progression criteria at the time; 18.2% of patients had progressive bone disease In stage 2, 7.7% of patients had PR by RECIST, 41.7% had SD (assessed by clinical or radiographic data)	Aragon-Ching et al (2009) [78]
Sorafenib, phase 2 chemotherapy-naïve CRPC (N=57)	20% of patients had SD by PSA, 3.6% had PSA responses, 38.1% had PSA progression	7.3% of patients had SD by RECIST 8 weeks median PFS, 13% 1-year PFS rate (progression by PSA or RECIST) Estimated 68% 1-year OS rate	Steinbild et al (2007) [15]
Sunitinib, phase 2 CRPC (N=34)	PSA response ($\geq 50\%$ decline) was the primary end point: 5.8% of patients had PSA responses, 44.1% had stable PSA at week 12 Improvements in clinical symptoms, pain, CT scan and/or bone scan observed in patients with rising PSA values	3.3% of patients had PR by RECIST, 60% had SD 3 patients showed improvement in bone scan	Michaelson et al (2009) [18]
Sunitinib, phase 2 docetaxel pretreated mCRPC (N=36)	12.1% of patients had PSA responses Discordant PSA increases seen in 45.5% of patients with improvements in pain scores	11.1% of patients had $\geq 30\%$ declines by RECIST; 44.4% had some tumour shrinkage Decline in pain score ≥ 2 points in 13.6% of patients, ≥ 1 point in 50%	Sonpavde et al (2010) [19]

(m)CRPC, (metastatic) castration-resistant prostate cancer; SD, stable disease; PR, partial response; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; OS, overall survival; CT, computed tomography

all survival benefit has been found. The lack of survival benefit may reflect the development of evasive resistance during treatment. Upregulation of MET signalling in tumours is a potential mechanism of this resistance. Preclinical and clinical results indicate that targeting of MET and VEGF signalling together has advantages over targeting either pathway alone. The benefit of simultaneous inhibi-

tion of MET and VEGFR is evident in the resolution of bone lesions visible in bone scans of many CRPC patients treated with cabozantinib, which blocks both pathways. The evaluation of clinical benefit in trials of angiogenesis inhibitors in CRPC is confounded by rising PSA levels in some patients, despite evidence of clinical benefit and/or lack of tumour progression. Clinical and preclinical data

suggest that rising PSA may be a consequence of antiangiogenic TKI therapy and may not be useful for assessing the efficacy of these agents in CRPC. Other measures of treatment efficacy, such as bone scans or CTCs, may be more meaningful in future clinical trials for assessment of agents that target MET and VEGF signalling pathways in CRPC.

References

- American Cancer Society (ACS) (2010) Cancer facts and figures 2010. American Cancer Society, Atlanta, GA
- Leo S, Accettura C, Lorusso V (2011) Castration-resistant prostate cancer: targeted therapies. *Chemotherapy* 57:115–127
- Scher HI, Halabi S, Tannock I et al (2008) 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* 26:1148–1159
- Ruch JM, Hussain MH (2011) Evolving therapeutic paradigms for advanced prostate cancer. *Oncology (Williston Park)* 25:496–504, 508
- Bergers G, Benjamin LE (2003) Tumorigenesis and the angiogenic switch. *Nat Rev Cancer* 3:401–410
- Hanahan D, Folkman J (1996) Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell* 86:353–364
- Folkman J (1971) Tumor angiogenesis: therapeutic implications. *N Engl J Med* 285:1182–1186
- Ferrer FA, Miller LJ, Andrawis RI et al (1997) Vascular endothelial growth factor (VEGF) expression in human prostate cancer: in situ and in vitro expression of VEGF by human prostate cancer cells. *J Urol* 157:2329–2333
- Duque JL, Loughlin KR, Adam RM et al (1999) Plasma levels of vascular endothelial growth factor are increased in patients with metastatic prostate cancer. *Urology* 54:523–527
- Weidner N, Carroll PR, Flax J et al (1993) Tumor angiogenesis correlates with metastasis in invasive prostate carcinoma. *Am J Pathol* 143:401–409
- Gettman MT, Pacelli A, Slezak J et al (1999) Role of microvessel density in predicting recurrence in pathologic stage T3 prostatic adenocarcinoma. *Urology* 54:479–485
- Bok RA, Halabi S, Fei DT et al (2001) Vascular endothelial growth factor and basic fibroblast growth factor urine levels as predictors of outcome in hormone-refractory prostate cancer patients: a cancer and leukemia group B study. *Cancer Res* 61:2533–2536
- George DJ, Halabi S, Shepard TF et al (2001) 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* 7:1932–1936
- De Lorenzo G, Figg WD, Fossa SD et al (2008) Combination of bevacizumab and docetaxel in docetaxel-pretreated hormone-refractory prostate cancer: A Phase 2 Study. *European Urology* 54:1089–1096
- Steinbild S, Mross K, Frost A et al (2007) 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* 97:1480–1485
- Dahut WL, Scripture C, Posadas E et al (2008) A phase II clinical trial of sorafenib in androgen-independent prostate cancer. *Clin Cancer Res* 14:209–214
- Adelberg D, Karakunnel JJ, Gulley JL et al (2010) A phase II study of cediranib in post-docetaxel, castration-resistant prostate cancer (CRPC). 2010 ASCO Genitourinary Cancer Symposium, abstr 63
- Michaelson MD, Regan MM, Oh WK et al (2009) Phase II study of sunitinib in men with advanced prostate cancer. *Ann Oncol* 20:913–920
- Sonpavde G, Periman PO, Bernold D et al (2010) Sunitinib malate for metastatic castration-resistant prostate cancer following docetaxel-based chemotherapy. *Ann Oncol* 21:319–324
- Ryan CJ, Stadler WM, Roth B et al (2007) 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 (HRPC). *Invest New Drugs* 25:445–451
- Kelly WK, Halabi S, Carducci MA et al (2010) A randomized, double-blind, placebo-controlled phase III trial comparing docetaxel, prednisone, and placebo with docetaxel, prednisone, and bevacizumab in men with metastatic castration-resistant prostate cancer (mCRPC): survival results of CALGB 90401. *J Clin Oncol* 28[suppl 18]:abstr LBA4511
- Michaelson MD, Oudard S, Ou Y et al (2011) Randomized placebo-controlled, phase III trial of sunitinib in combination with prednisone (SU+P) versus prednisone (P) alone in men with progressive metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 29[suppl 15]:4515
- Ebos JM, Kerbel RS (2011) Antiangiogenic therapy: impact on invasion, disease progression, and metastasis. *Nat Rev Clin Oncol* 8:210–221. Erratum in 8:316; 8:221
- Burger RA, Brady MF, Bookman MA et al (2010) Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): a Gynecologic Oncology Group study. *J Clin Oncol* 28[suppl 18]:abstr LBA1
- Hurwitz H, Fehrenbacher L, Novotny W et al (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 350:2335–2342
- Motzer RJ, Hutson TE, Tomczak P et al (2009) Overall survival and updated results for sunitinib compared with interferon alpha in patients with metastatic renal cell carcinoma. *J Clin Oncol* 27:3584–3590
- Escudier B, Eisen T, Stadler WM et al (2007) Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 356:125–134
- Gerstner ER, Chen PJ, Wen PY et al (2010) Infiltrative patterns of glioblastoma spread detected via diffusion MRI after treatment with cediranib. *Neuro Oncol* 12:466–472
- de Groot JF, Fuller G, Kumar AJ et al (2010) Tumor invasion after treatment of glioblastoma with bevacizumab: radiographic and pathologic correlation in humans and mice. *Neuro Oncol* 12:233–242
- Casanovas O, Hicklin DJ, Bergers G, Hanahan D (2005) Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. *Cancer Cell* 8:299–309
- Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. *Cell* 144:646–674
- Ebos JM, Lee CR, Cruz-Munoz W et al (2009) Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. *Cancer Cell* 15:232–239
- Pàez-Ribes M, Allen E, Hudock J et al (2009) Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. *Cancer Cell* 15:220–231
- di Tomaso E, Snuderl M, Kamoun WS et al (2011) Glioblastoma recurrence after cediranib therapy in patients: lack of "rebound" revascularization as mode of escape. *Cancer Res* 71:19–28
- Sennino B, Naylor RM, Tabruyn SP et al (2009) Reduction of tumor invasiveness and metastasis and prolongation of survival of RIP-Tag2 mice after inhibition of VEGFR plus c-Met by XL184. *Mol Cancer Ther* 8[suppl 1]:A13
- You WK, Sennino B, Williamson CW et al (2011) VEGF and c-Met blockade amplify angiogenesis inhibition in pancreatic islet cancer. *Cancer Res* 71:4758–4768
- Christensen JG, Burrows J, Salgia R (2005) c-Met as a target for human cancer and characterization of inhibitors for therapeutic intervention. *Cancer Lett* 225:1–26
- You WK, McDonald DM (2008) The hepatocyte growth factor/c-Met signaling pathway as a therapeutic target to inhibit angiogenesis. *BMB Rep* 41:833–839
- Cecchi F, Rabe DC, Bottaro DP (2010) Targeting the HGF/Met signalling pathway in cancer. *Eur J Cancer* 46:1260–1270
- Pennacchietti S, Michieli P, Galluzzo M et al (2003) Hypoxia promotes invasive growth by transcriptional activation of the met protooncogene. *Cancer Cell* 3:347–346
- Kitajima Y, Ide T, Ohtsuka T, Miyazaki K (2008) Induction of hepatocyte growth factor activator gene expression under hypoxia activates the hepatocyte growth factor/c-Met system via hypoxia inducible factor-1 in pancreatic cancer. *Cancer Sci* 99:1341–1347
- Shojaei F, Lee JH, Simmons BH et al (2010) HGF/c-Met acts as an alternative angiogenic pathway in sunitinib-resistant tumors. *Cancer Res* 70:10090–10100
- Nakashiro K, Hayashi Y, Oyasu R (2003) Immunohistochemical expression of hepatocyte growth factor and c-Met/HGF receptor in benign and malignant human prostate tissue. *Oncol Rep* 10:1149–1153
- Pisters LL, Troncoso P, Zhou HE et al (1995) c-met proto-oncogene expression in benign and malignant human prostate tissues. *J Urol* 154:293–298
- Zhu X, Humphrey PA (2000) Overexpression and regulation of expression of scatter factor/hepatocyte growth factor in prostatic carcinoma. *Urology* 56:1071–1074
- Humphrey PA, Zhu X, Zarnegar R et al (1995) Hepatocyte growth factor and its receptor (c-MET) in prostatic carcinoma. *Am J Pathol* 147:386–396
- Knudsen BS, Gmyrek GA, Inra J et al (2002) High expression of the Met receptor in prostate cancer metastasis to bone. *Urology* 60:1113–1117
- Zhang S, Zhou HE, Osunkoya AO et al (2010) Vascular endothelial growth factor regulates myeloid cell leukemia-1 expression through neuropilin-1-dependent activation of c-MET signaling in human prostate cancer cells. *Mol Cancer* 9:9
- Humphrey PA, Halabi S, Picus J et al (2006) Prognostic significance of plasma scatter factor/hepatocyte growth factor levels in patients with metastatic hormone-refractory prostate can-

- cer: results from cancer and leukemia group B 150005/9480. *Clin Genitourin Cancer* 4:269–274
50. Sirotnak FM, She Y, Khokhar NZ et al (2004) Microarray analysis of prostate cancer progression to reduced androgen dependence: studies in unique models contrasts early and late molecular events. *Mol Carcinog* 41:150–163
 51. Verras M, Lee J, Xue H et al (2007) The androgen receptor negatively regulates the expression of c-Met: implications for a novel mechanism of prostate cancer progression. *Cancer Res* 67:967–975
 52. Maeda A, Nakashiro K, Hara S et al (2006) Inactivation of AR activates HGF/c-Met system in human prostatic carcinoma cells. *Biochem Biophys Res Commun* 347:1158–1165
 53. Pfeiffer MJ, Smit FP, Sedelaar JP, Schalken JA (2011) Steroidogenic enzymes and stem cell markers are upregulated during androgen deprivation in prostate cancer. *Mol Med* 17:657–664
 54. Morrissey C, Vassella RL (2007) The role of tumor microenvironment in prostate cancer bone metastasis. *J Cell Biochem* 101:873–886
 55. Cook RJ, Coleman R, Brown J et al (2006) Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. *Clin Cancer Res* 12(11 Pt 1):3361–3367
 56. Leonardi R, Caltabiano R, Loreto C (2010) The immunolocalization and possible role of c-Met (MET, hepatic growth factor receptor) in the developing human fetal mandibular condyle. *Acta Histochem* 112:482–488
 57. Inaba M, Koyama H, Hino M et al (1993) Regulation of release of hepatocyte growth factor from human promyelocytic leukemia cells, HL-60, by 1,25-dihydroxyvitamin D₃, 12-O-tetradecanoylphorbol 13-acetate, and dibutylryl cyclic adenosine monophosphate. *Blood* 82:53–59
 58. Grano M, Galimi F, Zambonin G et al (1996) Hepatocyte growth factor is a coupling factor for osteoclasts and osteoblasts in vitro. *Proc Natl Acad Sci U S A* 93:7644–7648
 59. Standal T, Abildgaard N, Fagerli UM et al (2007) HGF inhibits BMP-induced osteoblastogenesis: possible implications for the bone disease of multiple myeloma. *Blood* 109:3024–3030
 60. Reichert JC, Quent VM, Burke LJ et al (2010) Mineralized human primary osteoblast matrices as a model system to analyse interactions of prostate cancer cells with the bone microenvironment. *Biomaterials* 31:7928–7936
 61. Ono K, Kamiya S, Akatsu T et al (2006) Involvement of hepatocyte growth factor in the development of bone metastasis of a mouse mammary cancer cell line, BALB/c-MC. *Bone* 39:27–34
 62. Street J, Bao M, deGuzman L et al (2002) Vascular endothelial growth factor stimulates bone repair by promoting angiogenesis and bone turnover. *Proc Natl Acad Sci U S A* 99:9656–9661
 63. Zelzer E, Olsen BR (2005) Multiple roles of vascular endothelial growth factor (VEGF) in skeletal development, growth, and repair. *Curr Top Dev Biol* 65:169–687
 64. Dai J, Kitagawa Y, Zhang J et al (2004) Vascular endothelial growth factor contributes to the prostate cancer-induced osteoblast differentiation mediated by bone morphogenetic protein. *Cancer Res* 64:994–999
 65. Jacobsen KA, Al-Aql ZS, Wan C et al (2008) Bone formation during distraction osteogenesis is dependent on both VEGFR1 and VEGFR2 signaling. *J Bone Miner Res* 23:596–609
 66. Niida S, Kaku M, Amano H et al (1999) Vascular endothelial growth factor can substitute for macrophage colony-stimulating factor in the support of osteoclastic bone resorption. *J Exp Med* 190:293–298
 67. Beamer B, Hettrich C, Lane J (2009) Vascular endothelial growth factor: an essential component of angiogenesis and fracture healing. *HSS J* 6:85–94
 68. Schipani E, Maes C, Carmeliet G, Semenza GL (2009) Regulation of osteogenesis-angiogenesis coupling by HIFs and VEGF. *J Bone Miner Res* 24:1347–1353
 69. Yap TA, Olmos D, Brunetto AT et al (2011) Phase I trial of a selective c-MET inhibitor ARQ 197 incorporating proof of mechanism pharmacodynamic studies. *J Clin Oncol* 29:1271–1279
 70. Mekhail T, Rich T, Rosen L et al (2009) Final results: a dose escalation phase I study of ARQ 197, a selective c-Met inhibitor, in patients with metastatic solid tumors. *J Clin Oncol* 27[suppl 15]:3548
 71. Hussain M, Smith MR, Sweeney C et al (2011) Cabozantinib (XL184) in metastatic castration-resistant prostate cancer (mCRPC): results from a phase II randomized discontinuation trial. *J Clin Oncol* 29[suppl 15]:abstr 4516
 72. Smith DC, Smith MR, Small EJ et al (2011) Phase 2 study of cabozantinib (XL184) in a cohort of patients with castration-resistant prostate cancer (CRPC) and measurable soft tissue disease. Poster presented at: 2011 ASCO Genitourinary Symposium, 17–19 February 2011, Orlando, FL, Abstract 127
 73. Amgen, Inc. (2000) AMG 102 in combination with mitoxantrone and prednisone in subjects with previously treated castrate resistant prostate cancer. In: *ClinicalTrials.gov* [Internet]. National Library of Medicine (US), Bethesda, MD. [cited 2011 Aug 23]. Available from: <http://clinicaltrials.gov/show/NCT00770848> NLM Identifier: NCT00770848
 74. Amgen, Inc. (2011) Amgen outlines strategy, growth objectives and capital allocation plans. April 21. Web, August 23, 2011. http://www.amgen.com/media/media_pr_detail.jsp?year=2011&releaseID=1553298
 75. Smith DC, Dunn RL, Strawderman MS, Pienta KJ (1998) Change in serum prostate-specific antigen as a marker of response to cytotoxic therapy for hormone-refractory prostate cancer. *J Clin Oncol* 16:1835–1843
 76. Armstrong AJ, Garrett-Mayer E, Ou Yang YC et al (2007) Prostate-specific antigen and pain surgery analysis in metastatic hormone-refractory prostate cancer. *J Clin Oncol* 25:3965–3970
 77. Hussain M, Goldman B, Tangen C et al (2009) Prostate-specific antigen progression predicts overall survival in patients with metastatic prostate cancer: data from Southwest Oncology Group trials 9346 (Intergroup Study 0162) and 9916. *J Clin Oncol* 27:2450–2456
 78. Aragon-Ching JB, Jain L, Gulley JL et al (2009) Final analysis of a phase II trial using sorafenib for metastatic castration-resistant prostate cancer. *BJU Int* 103:1636–1640
 79. Chi KN, Ellard SL, Hotte SJ et al (2008) A phase II study of sorafenib in patients with chemo-naive castration-resistant prostate cancer. *Ann Oncol* 19:746–751
 80. Li Y, Sikes RA, Malaeb BS et al (2010) Osteoblasts can stimulate prostate cancer growth and transcriptionally down-regulate PSA expression in cell line models. *Urol Oncol* (in press)
 81. Sabbatini P, Larson SM, Kremer A et al (1999) Prognostic significance of extent of disease in bone in patients with androgen-independent prostate cancer. *J Clin Oncol* 17:948–957
 82. Morris MJ, Jia X, Larson SM et al (2008) Post-treatment serial bone scan index (BSI) as an outcome measure predicting survival. Poster presented at: 2008 ASCO Genitourinary Symposium, 14–16 February 2008, San Francisco, CA, abstract 188
 83. Scher HI, Warren M, Heller G (2007) The association between measures of progression and survival in castrate-metastatic prostate cancer. *Clin Cancer Res* 13:1488–1492
 84. Scher HI, Mazumdar M, Kelly WK (1996) Clinical trials in relapsed prostate cancer: defining the target. *J Natl Cancer Inst* 88:1623–1634
 85. Erdi YE, Humm JL, Imbricco et al (1997) Quantitative bone metastases analysis based on image segmentation. *J Nucl Med* 38:1401–1406
 86. Sadik M, Jakobsson D, Olofsson F et al (2006) A new computer-based decision-support system for the interpretation of bone scans. *Nucl Med Commun* 27:417–423
 87. Danila DC, Heller G, Gignac GA et al (2007) Circulating tumor cell number and prognosis in progressive castration-resistant prostate cancer. *Clin Cancer Res* 13:7053–7058
 88. Morgan TM, Lange PH, Porter MP et al (2009) Disseminated tumor cells in prostate cancer patients after radical prostatectomy and without evidence of disease predicts biochemical recurrence. *Clin Cancer Res* 15:677–683
 89. de Bono JS, Scher HI, Montgomery RB et al (2008) Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin Cancer Res* 14:6302–6309
 90. Olmos D, Arkenau HT, Ang JE et al (2009) Circulating tumour cell (CTC) counts as intermediate end points in castration-resistant prostate cancer (CRPC): a single-centre experience. *Ann Oncol* 20:27–33
 91. Scher HI, Jia X, de Bono JS et al (2009) Circulating tumour cells as prognostic markers in progressive, castration-resistant prostate cancer: a reanalysis of IMMC38 trial data. *Lancet Oncol* 10:233–239
 92. Scher HI, Heller G, Molina A et al (2011) Evaluation of circulating tumor cell (CTC) enumeration as an efficacy response biomarker of overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC): planned final analysis (FA) of COU-AA-301, a randomized double-blind, placebo-controlled phase III study of abiraterone acetate (AA) plus low-dose prednisone (P) post docetaxel. *J Clin Oncol* 29[suppl 18]:abstr LBA4517
 93. Danila DC, Fleisher M, Scher HI (2011) Circulating tumor cells as biomarkers in prostate cancer. *Clin Cancer Res* 17:3903–3912