Research in castration-resistant prostate cancer: what does the future hold?

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ABSTRACT

Prostate cancer (PCa) is the most common non-skin cancer diagnosed in North America, and it affects 1 in 6 men. Patients with recurrent or metastatic PCa will inevitably develop castration-resistant disease after an initial period of hormone responsiveness. The standard first-line treatment for men with castration-resistant PCa (CRPC) is docetaxel, but further treatment options are limited. This review summarizes the research being conducted in CRPC, with specific regard to immunotherapy and to novel targeted therapies directed against the androgen axis, vascular endothelial growth factor, chaperone proteins, the phosphoinositide 3 kinase/Akt/phosphatase and tensin homolog/mammalian target of rapamycin pathway, and endothelin-1.

KEY WORDS

Castration-resistant prostate cancer, novel therapy, targeted therapy

1. INTRODUCTION

Men with recurrent or metastatic prostate cancer (PCa) will, invariably, develop castration resistance after an initial period of hormone responsiveness. Historically, the treatment arsenal for men with castration-resistant PCa (CRPC) has been limited to those interventions that afford some modicum of symptomatic benefit. Treatments approved for use in symptomatic men with CRPC include mitoxantrone [1], radioactive isotopes [2], and the bisphosphonate zoledronic acid [3]. Docetaxel is the only approved systemic agent that has been shown to improve overall survival [OS (median improvement: 2.4 months over mitoxantrone)] [4,5]. Recently, cabazitaxel, a novel taxane, was reported to have a median OS benefit of 2.4 months over mitoxantrone and prednisone in patients progressing after docetaxel, although regulatory approval is still pending [6]. Given the fact that PCa is the most commonly diagnosed non-skin cancer in North America [7] and given the paucity of treatment options that afford an OS benefit, significant preclinical and clinical research is being conducted in an effort to change the situation.

Clinicians are now poised for significant potential change when it comes to the management of CRPC. An increase in the understanding of the biologic underpinnings of cancer in general, and of PCa specifically, has led to rational drug development, and the resulting drugs are currently being tested in both early- and late-phase clinical trials. Novel therapies that target androgen receptor signalling, the vascular endothelial growth factor pathway, apoptosis, chaperone proteins, the insulin-like growth factor pathway, and the phosphoinositide 3 kinase (PI3K)/Akt/phosphatase and tensin homolog (PTEN)/mammalian target of rapamycin (mTOR) pathway have been developed and are being evaluated. Beyond that, therapeutics focused on bone targeting, novel cytotoxic chemotherapies, and drug combinations are also under investigation.

This article focuses on some of the current concepts behind targeted therapy for CRPC, with a focus on novel agents that are currently in late-phase clinical trials or that target unique pathways.

2. DISCUSSION

2.1 Androgen Receptor Signalling

For many patients with recurrent or metastatic disease, hormonal therapy has the ability to induce long-term disease control, but the development of castration-resistant disease is inevitable. When CRPC develops, either (or both of) rising prostate-specific antigen (PSA) and radiologic progression is seen despite castrate levels of testosterone [8,9]. Historically, this circumstance was termed "hormone refractory disease." It has long been observed, however, that men who progress after first-line hormonal maneuvers will often have a PSA and clinical response to second-line hormonal treatments, and thus the term "hormone refractory" is no longer appropriate.

Clinical response to second-line hormonal maneuvers was initially thought to be solely related to extragonadal androgen production, but additional

mechanisms potentially underlie such responses. Several studies have demonstrated amplification and increased expression of the androgen receptor (AR) in CRPC tissue [10–12], and *in vitro* and *in vivo* studies have also shown that, for the evolution of CRPC, increased expression of the AR is necessary [11]. Prostate cancer cells also possess the biochemical machinery to synthesize androgens by an autocrine/paracrine mechanism [13–16]. Finally, AR splice variants lacking the ligand binding domain have been observed to be constitutively active, independent of the presence of ligand [17]. Over the last several years, an area of active research has been the development of more potent inhibitors of extragonadal androgen production and of small-molecule antagonists of the AR [18].

Abiraterone acetate (AA) is an orally administered inhibitor of the cytochrome P450 enzyme, CYP17A1. The CYP17A1 enzyme has dual functions both as a 17α-hydroxylase and a $C_{17,20}$-lase, both functions being necessary for the conversion of cholesterol precursors into androgen. A phase I clinical trial has demonstrated a high degree of tolerance [19], and the reported toxicities were, as anticipated, related to mineralocorticoid excess (hypertension, hypokalemia, edema) and were easily controlled with co-administration of low doses of prednisone. Patient populations who were chemotherapy-naïve and those that had progressed post docetaxel were subsequently evaluated in several phase II clinical trials of AA.

In one such trial, 27 patients with CRPC who had never received chemotherapy received AA, and a PSA decline of more than 50% was observed in 85% of those patients [20]. Another phase II trial evaluated AA in 47 patients who were previously treated with docetaxel [21]. Declines in PSA of more than 50% were observed in 51% of the patients, and partial radiologic responses were observed in 6 of 35 patients (17%) with measurable disease. Responses were durable, with 17 patients remaining on therapy for more than 6 months, and treatment continued for a median duration of 167 days. Another phase II trial evaluated AA in patients who were heavily pretreated [22]. Patients who had previously been exposed to high doses of ketoconazole (a less-specific inhibitor of CYP450 enzyme) appeared to be less responsive to abiraterone: as compared with 55% of patients who had not received prior ketoconazole, 30% of those who did experienced a greater-than-50% PSA decline.

A multicentric randomized double-blind placebo-controlled phase III trial evaluating abiraterone in patients with metastatic CRPC and with progression after docetaxel chemotherapy has completed accrual (see NCT00638690 at www.ClinicalTrials.gov). The trial randomized 1158 patients 2:1 in favour of AA. The primary endpoint is overall survival. A second phase III trial with AA has also completed accrual. Approximately 1000 minimally symptomatic chemotherapy-naïve patients were randomized to AA or placebo (see NCT00887198 at www.ClinicalTrials.gov) with primary endpoints of OS and progression-free survival.

Another novel anti-androgen under development is MDV3100. Compared with bicalutamide, this drug is a more potent AR antagonist, and it possesses no agonistic activity. In PCa models and clinically, it is often observed that bicalutamide can have agonistic effects on the AR [11] as a result of nuclear translocation, DNA binding, and co-activator recruitment. In contrast, when MDV3100 binds the AR, nuclear translocation is inefficient, and DNA binding is completely inhibited. A first-in-humans phase I/II dose-escalation study was recently reported. At 12 weeks, 57% of chemotherapy-naïve patients and 45% of pretreated patients had a 50% or better PSA decline. Dose-limiting toxicities included seizures, but these were not observed at lower doses that were still associated with clinical activity [23]. A phase III trial is currently recruiting patients with CRPC who have progressed after docetaxel and is randomizing patients 2:1 in favour of MDV3100, with a planned accrual of 1200 patients and a primary endpoint of OS (see NCT00974311 at www.ClinicalTrials.gov).

2.2 Vascular Endothelial Growth Factor and Its Receptor

Growth beyond a few millimetres and the ability to metastasize depend on a malignant tumour's ability to recruit new vasculature through angiogenesis. The vascular endothelial growth factor (VEGF) pathway is a well-characterized mediator of angiogenesis, and many agents have been developed that target the VEGF pathway and receptor. Elevated levels of VEGFR2 are seen in human PCas [24], and increased plasma levels of VEGF have been associated with poor prognosis and disease progression [25].

Bevacizumab is a monoclonal antibody directed against VEGFA that causes potent inhibition of VEGF receptor (VEGFR) signalling and angiogenesis. Bevacizumab has been evaluated and approved for use in renal, colorectal, breast, and lung cancer. In PCa, bevacizumab has been trialed in combination with docetaxel with encouraging early-phase results [26]; however, a recent press release from Roche has stated that the Cancer and Leukemia Group B (CALGB) randomized placebo-controlled phase III trial of docetaxel with or without bevacizumab has failed to meet its primary endpoint of improved OS (see NCT00110214 at www.ClinicalTrials.gov).

Aflibercept ("VEGF trap") is a recombinantly-produced fusion protein consisting of human VEGFR extracellular domains fused to the Fc portion of human immunoglobulin G1. By binding to and inactivating the circulating factors VEGF and VEGFB, aflibercept prevents them from binding to VEGFR1 and 2 [27]. Phase I studies have shown that the combination of aflibercept and docetaxel is safe [28], and a phase III placebo-controlled trial assessing the effect

of docetaxel with or without aflibercept is underway (see NCT00519285 at www.ClinicalTrials.gov).

Sunitinib is an orally administered multi-targeted tyrosine kinase inhibitor of VEGFR, platelet-derived growth factor receptor, and Kit. A phase II trial of sunitinib given after patients had progressed on docetaxel showed a PSA decline of 50% or more in 12% of patients and of 30% or more in 21% [29]. Despite the activity, 53% of patients discontinued treatment secondary to toxicities, and 2 treatment-related deaths occurred. A phase III trial of sunitinib as second-line treatment after docetaxel is currently accruing (see NCT00676650 at www.ClinicalTrials.gov).

2.3 Chaperone Proteins

A number of chaperone proteins have been identified as being of interest in CRPC, including clusterin. Clusterin exists as both an intracellular truncated form that is proapoptotic [30] and as a cytoplasmic and secretory form that is antiapoptotic [31]. In cancer, clusterin has been largely defined in its role of inhibiting apoptosis. After therapeutic stress, clusterin is activated and functions as a cytoprotective chaperone, similar to an adenosine triphosphate–independent small heat shock protein. It is transcriptionally activated by heat shock factor 1 [32]. Bax is a critical proapoptotic member of the Bcl2 family, and clusterin has been shown to inhibit activated Bax, thereby inhibiting apoptosis [31]. Clusterin has also been associated with activation of the PI3K/Akt pathway through the megalin cell-surface receptor [33]. In cancer models, forced overexpression of clusterin confers resistance to radiation, hormone therapies, and chemotherapy. Further, inhibition of clusterin enhances apoptotic death from those same treatment modalities [34]. In preclinical models of PCa, clusterin has been associated with androgen-independent progression [35]. In clinical samples, increased expression of clusterin is associated with increasing Gleason grade and castration-resistant disease [36]. Taken together, these findings make clusterin an attractive target in the treatment of CRPC.

The phosphorothioate antisense molecule OGX-011 inhibits translation of clusterin messenger RNA, thereby decreasing secretory clusterin expression *in vitro* and *in vivo*. In phase I trials, it has been demonstrated that OGX-011 can inhibit expression of clusterin in PCa tissue and that the compound can be delivered safely with chemotherapy [37,38]. A randomized phase II trial of OGX-011 (given with either mitoxantrone or docetaxel) in patients who had progressed either on or within 3 months of treatment with docetaxel was reported at the 2008 American Society of Clinical Oncology (ASCO) annual meeting [39]. In 27% of patients who received mitoxantrone with OGX-011, a PSA decline of 50% or more was observed, and the median OS in that group was 11.4 months. In the group that received docetaxel with OGX-011, 40% experienced a 50% or greater drop in PSA, and median OS was 14.7 months. A second randomized phase II trial was presented at the 2009 ASCO annual meeting. In that study, 82 chemotherapy-naïve patients with metastatic CRPC were randomized to receive first-line docetaxel either with or without OGX-011 [40]. Although there was no difference PSA decline between groups, fewer patients had progression as best response, and the group receiving OGX-011 with docetaxel experienced a longer time to progression. Mature results from that study demonstrated a median OS of 16.9 months in the docetaxel-alone group as compared with 27.5 months in the docetaxel with OGX-011 group [41]. A phase III trial expected to commence later in 2010 will compare docetaxel and OGX-011 with docetaxel alone in patients with chemotherapy-naïve metastatic CRPC. The primary endpoint will be OS.

2.4 PI3K/Akt/mTOR

Several cell-surface receptors that activate the downstream PI3K/AKT/MTOR signal transduction pathway to regulate survival, growth, proliferation, and angiogenesis—epidermal growth factor receptor, platelet-derived growth factor, insulin-like growth factor receptor (IGFR), insulin receptor, and interleukin 6 receptors—have been implicated in cancer progression [42,43]. In PCa, activation of the PI3K/Akt/MTOR pathway has been associated with ligand-independent activation of the AR and with androgen-independent progression of PCa [42,44]. The tumour-suppressor gene *PTEN,* frequently deleted in PCa, normally serves to negatively regulate the PI3K/Akt survival pathway [45]. A number of approaches to targeting this pathway are in early-phase clinical development in PCa. These approaches include activity against cell-surface receptors [for example, monoclonal antibodies to IGF1R (see NCT00313781 at www.ClinicalTrials.gov) [46]], PI3K, Akt, and MTOR [47] (see NCT00110188, NCT00629525, NCT00574769, NCT00085566, NCT00703625, and NCT00703170 at www.ClinicalTrials.gov) either as single agents or in combination with other agents.

2.5 Endothelin 1

Prostate cancer has a propensity to metastasize to bone, and so targeting the pathways that mediate bone progression is a rational approach. Endothelins (ETS) are 21-amino-acid peptides that are elevated in men with metastatic PCa and that are known mediators of the osteoblastic response of bone to metastatic disease [48].

Endothelin 1 preferentially binds to endothelin A (ETA), and ETA signalling has been associated with proliferation, antiapoptotic effects, and pain. Atrasentan is an orally bioavailable competitive inhibitor of ET1. Biologic effects were observed in early-phase studies [49]; however, two phase III trials have failed to demonstrate an improvement in time to progression despite evidence of decreased bone turnover [50,51]. Development

of atrasentan in combination with docetaxel continues. Phase I/II studies of this combination have resulted in high rates of febrile neutropenia (16%–25%) and a shorter-than-expected median OS [52]. Nevertheless, the Southwest Oncology Group is conducting a phase III trial comparing docetaxel–prednisone with docetaxel–prednisone–atrasentan in 930 patients with metastatic CRPC; the primary endpoint is OS (see NCT00134056 at www.ClinicalTrials.gov).

A more specific inhibitor of ETA, ZD4054, is currently in testing. A 3-arm randomized phase II trial assessing 2 doses of AD4054 as compared with placebo showed no difference in the primary endpoint of progression, but did demonstrate an OS benefit of more than 6 months in favour of the treatment arms [53]. Consequently, 3 phase III trials are currently underway: ZD4054 versus placebo in CRPC with no metastases (see NCT00626548 at www.ClinicalTrials.gov), in CRPC with bone metastases that have no or minimal associated symptoms (see NCT00554229 at www.ClinicalTrials.gov), and in patients receiving docetaxel (see NCT00617669 at www.ClinicalTrials.gov).

2.6 Immunotherapy

Another rapidly evolving area in the treatment of CRPC is immunotherapy, wherein the goal is to harness the body's own immune system to elicit an antitumour effect. To properly immunize a patient with a tumour-specific antigen, inducing an antitumour effect, antigen-presenting cells [APCs (such as dendritic cells)] must process and present the antigens to T cells.

Sipuleucel-T is dendritic cell–based vaccine designed to stimulate T-cell immunity against prostatic acid phosphatase (PAP), which is expressed in benign and malignant prostate epithelia alike. Vaccine preparation requires patients to undergo a 1.5–2.0 blood-volume mononuclear cell leucapheresis. The APCs are extracted and cultured with a fusion protein that consists of PAP linked to granulocyte–macrophage colony–stimulating factor (GM-CSF). As a result, the APCs are activated, and upon re-introduction to the patient, they load and process the PAP antigen for presentation to the T cell.

Phase I and II trials have demonstrated that this approach is feasible, and sipuleucel-T testing in phase III trials produced evidence of antitumour activity [54]. Two small, identically designed randomized phase III trials (double-blind and placebo-controlled) have evaluated sipuleucel-T in men with metastatic CRPC. The primary endpoint of PFS was not statistically different between the treatment groups, but OS was statistically improved in the treatment group (as compared with placebo), showing a median OS benefit of 4.5 months [55]. The data from these trials were compiled and evaluated together, with the result that the OS benefit was maintained, with a 33% reduction in the risk of death in the treatment group [56]. Updated results from a larger 500-patient phase III trial were reported at the 2010 ASCO genitourinary symposium. That trial was designed with OS as the primary endpoint, and it demonstrated a 4.1-month survival advantage for the patients treated with sipuleucel-T [57]. Those results provide a "proof of principle" demonstration of clinical benefit and the viability of an active immunotherapy approach to cancer.

Other vaccine approaches have been less successful. The GVAX (GM-CSF gene-modified tumour) vaccine uses whole cells as an antigen source to provoke an immune response to multiple antigens. Phase I/II trials demonstrated safety [58], but two phase III studies in men with CRPC both closed early. The first study randomized 408 patients to docetaxel with GVAX or to GVAX alone, and it was closed by the independent data monitoring committee after an imbalance of deaths was observed in the immunotherapy arm (see NCT00133224 at www.ClinicalTrials.gov). A second trial accrued 626 asymptomatic patients and randomized them to receive GVAX or docetaxel (see NCT00089856 at www.ClinicalTrials.gov); that trial also closed early after interim analysis determined that the study was unlikely to meet its primary endpoint.

3. SUMMARY

Knowledge of the mechanisms driving the development and progression of CRPC has increased exponentially in the last several years, resulting in highly rational drug design based on sound preclinical evidence. Significant inroads are therefore being made in the treatment of a disease that, to date, has had only one intervention that affords a survival benefit. Positive results from the AA and MDV3100 trials are hoped for, and some success has already been seen with novel cytotoxics and immunotherapy. However, those successes bring attendant issues of availability and cost to the health care system that will have to be addressed in the coming months and years.

4. REFERENCES

1. Tannock IF, Osoba D, Stockler MR, *et al*. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol* 1996;14:1756–64.
2. Oosterhof GO, Roberts JT, de Reijke TM, *et al*. Strontium(89) chloride versus palliative local field radiotherapy in patients with hormonal escaped prostate cancer: a phase III study of the European Organisation for Research and Treatment of Cancer, Genitourinary Group. *Eur Urol* 2003;44:519–26.
3. Saad F, Gleason DM, Murray R, *et al*. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002;94:1458–68.
4. Petrylak DP, Tangen CM, Hussain MH, *et al*. Docetaxel and estramustine compared with mitoxantrone and prednisone

for advanced refractory prostate cancer. *N Engl J Med* 2004;351:1513–20.
5. Tannock IF, de Wit R, Berry WR, *et al*. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502–12.
6. De Bono JS, Oudard S, Ozguroglu M, *et al.* for the TROPIC Investigators. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: final results of a multinational phase III trial (TROPIC) [abstract 4508]. *Proc Am Soc Clin Oncol* 2010;28:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74&abstractID=44106; cited June 14, 2010]
7. Jemal A, Siegel R, Ward E, *et al*. Cancer statistics, 2008. *CA Cancer J Clin* 2008;58:71–96.
8. Scher HI, Halabi S, Tannock I, *et al*. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the prostate cancer clinical trials working group. *J Clin Oncol* 2008;26:1148–59.
9. Heidenreich A, Aus G, Bolla M, *et al*. EAU guidelines on prostate cancer. *Eur Urol* 2008;53:68–80.
10. Linja MJ, Savinainen KJ, Saramaki OR, Tammela TL, Vessella RL, Visakorpi T. Amplification and overexpression of androgen receptor gene in hormone-refractory prostate cancer. *Cancer Res* 2001;61:3550–5.
11. Chen CD, Welsbie DS, Tran C, *et al*. Molecular determinants of resistance to antiandrogen therapy. *Nat Med* 2004;10:33–9.
12. Mohler JL, Gregory CW, Ford OH 3rd, *et al*. The androgen axis in recurrent prostate cancer. *Clin Cancer Res* 2004;10:440–8.
13. Titus MA, Schell MJ, Lih FB, Tomer KB, Mohler JL. Testosterone and dihydrotestosterone tissue levels in recurrent prostate cancer. *Clin Cancer Res* 2005;11:4653–7.
14. Stanbrough M, Bubley GJ, Ross K, *et al*. Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. *Cancer Res* 2006;66:2815–25.
15. Holzbeierlein J, Lal P, LaTulippe E, *et al*. Gene expression analysis of human prostate carcinoma during hormonal therapy identifies androgen-responsive genes and mechanisms of therapy resistance. *Am J Pathol* 2004;164:217–27.
16. Locke JA, Guns ES, Lubik AA, *et al*. Androgen levels increase by intratumoral *de novo* steroidogenesis during progression of castration-resistant prostate cancer. *Cancer Res* 2008;68:6407–15.
17. Hu R, Dunn TA, Wei S, *et al*. Ligand-independent androgen receptor variants derived from splicing of cryptic exons signify hormone-refractory prostate cancer. *Cancer Res* 2009;69:16–22.
18. Attar RM, Jeur–Kunkel M, Balog A, *et al*. Discovery of BMS-641988, a novel and potent inhibitor of androgen receptor signaling for the treatment of prostate cancer. *Cancer Res* 2009; 69:6522–30.
19. Attard G, Reid AH, Yap TA, *et al*. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *J Clin Oncol* 2008;26:4563–71.
20. Ryan C, Efstathios E, Smith M, *et al*. Phase II multicenter study of chemotherapy (chemo)–naïve castration-resistant prostate cancer (CRPC) not exposed to ketoconazole (keto), treated with abiraterone acetate (AA) plus prednisone [abstract 5046]. *Proc Am Soc Clin Oncol* 2009;27:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=65&abstractID=34693; cited June 8, 2010]
21. Reid AH, Attard G, Danila D, *et al*. A multicenter phase II study of abiraterone acetate (AA) in docetaxel pretreated castration-resistant prostate cancer (CRPC) patients (pts) [abstract 5047]. *Proc Am Soc Clin Oncol* 2009;27:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=65&abstractID=34016; cited June 8, 2010]
22. Danila DC, de Bono J, Ryan CJ, *et al*. Phase II multicenter study of abiraterone acetate (AA) plus prednisone therapy in docetaxel-treated castration-resistant prostate cancer (CRPC) patients (pts): impact of prior ketoconazole (keto) [abstract 5048]. *Proc Am Soc Clin Oncol* 2009;27:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=65&abstractID=31591; cited June 8, 2010]
23. Scher HI, Beer TM, Higano CS, *et al*. Antitumour activity of MDV3100 in a phase I/II study of castration-resistant prostate cancer (CRPC) [abstract 5011]. *Proc Am Soc Clin Oncol* 2009;27:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=65&abstractID=34746; cited June 8, 2010]
24. Huss WJ, Hanrahan CF, Barrios RJ, Simons JW, Greenberg NM. Angiogenesis and prostate cancer: identification of a molecular progression switch. *Cancer Res* 2001;61:2736–43.
25. George DJ, Halabi S, Shepard TF, *et al*. Prognostic significance of plasma vascular endothelial growth factor levels in patients with hormone-refractory prostate cancer treated on cancer and leukemia group B 9480. *Clin Cancer Res* 2001;7:1932–6.
26. Picus J, Halabi S, Rini B, *et al*. The use of bevacizumab (B) with docetaxel (D) and estramustine (E) in hormone refractory prostate cancer (HRPC): initial results of CALGB 90006 [abstract 1578]. *Proc Am Soc Clin Oncol* 2003;22:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=23&abstractID=101428; cited June 8, 2010]
27. Verheul HM, Hammers H, van Erp K, *et al*. Vascular endothelial growth factor trap blocks tumor growth, metastasis formation, and vascular leakage in an orthotopic murine renal cell cancer model. *Clin Cancer Res* 2007;13:4201–8.
28. Isambert N, Freyer G, Zanetta S, Falandry C, Soussan Lazard K, Fumoleau P. A phase I dose escalation and pharmacokinetic (PK) study of intravenous aflibercept (VEGF trap) plus docetaxel (D) in patients (pts) with advanced solid tumors: preliminary results [abstract 3599]. *Proc Am Soc Clin Oncol* 2008;26:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=30715; cited June 8, 2010]
29. Sonpavde G, Periman PO, Bernold D, *et al.* Sunitinib malate for metastatic castration-resistant prostate cancer following docetaxel-based chemotherapy. *Ann Oncol* 2010;21:319–24.
30. Leskov KS, Klokov DY, Li J, Kinsella TJ, Boothman DA. Synthesis and functional analyses of nuclear clusterin, a cell death protein. *J Biol Chem* 2003;278:11590–600.
31. Zhang H, Kim JK, Edwards CA, Xu Z, Taichman R, Wang CY. Clusterin inhibits apoptosis by interacting with activated Bax. *Nat Cell Biol* 2005;7:909–15.

32. Humphreys DT, Carver JA, Easterbrook–Smith SB, Wilson MR. Clusterin has chaperone-like activity similar to that of small heat shock proteins. *J Biol Chem* 1999;274:6875–81.
33. Ammar H, Closset JL. Clusterin activates survival through the phosphatidylinositol 3–kinase/Akt pathway. *J Biol Chem* 2008;283:12851–61.
34. Gleave M, Chi KN. Knock-down of the cytoprotective gene, clusterin, to enhance hormone and chemosensitivity in prostate and other cancers. *Ann N Y Acad Sci* 2005;1058:1–15.
35. Miyake H, Nelson C, Rennie PS, Gleave ME. Testosterone-repressed prostate message-2 is an antiapoptotic gene involved in progression to androgen independence in prostate cancer. *Cancer Res* 2006;60:170–6.
36. July LV, Akbari M, Zellweger T, Jones EC, Goldenberg SL, Gleave ME. Clusterin expression is significantly enhanced in prostate cancer cells following androgen withdrawal therapy. *Prostate* 2002;50:179–88.
37. Chi KN, Eisenhauer E, Fazli L, *et al*. 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* 2005;97:1287–96.
38. Chi KN, Siu LL, Hirte H, *et al*. A phase I study of OGX-011, a 2′-methoxyethyl phosphorothioate antisense to clusterin, in combination with docetaxel in patients with advanced cancer. *Clin Cancer Res* 2008;14:833–9.
39. Saad F, Hotte SJ, North SA, *et al*. A phase II randomized study of custirsen (OGX-011) combination therapy in patients with poor-risk hormone refractory prostate cancer (HRPC) who relapsed on or within six months of 1st-line docetaxel therapy [abstract 5002]. *Proc Am Soc Clin Oncol* 2008;26:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=32032; cited June 8, 2010]
40. Chi KN, Hotte SJ, Yu E, *et al*. A randomized phase II study of OGX-011 in combination with docetaxel and prednisone or docetaxel and prednisone alone in patients with metastatic hormone refractory prostate cancer (HRPC) [abstract 5069]. *Proc Am Soc Clin Oncol* 2007;25:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=47&abstractID=30401; cited June 8, 2010.
41. Chi KN, Hotte SJ, Yu E, *et al*. 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]. *Proc Am Soc Clin Oncol* 2009;27:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=65&abstractID=30398; cited June 8, 2010.
42. Mousses S, Wagner U, Chen Y, *et al*. Failure of hormone therapy in prostate cancer involves systematic restoration of androgen responsive genes and activation of rapamycin sensitive signaling. *Oncogene* 2001;20:6718–23.
43. Gera JF, Mellinghoff IK, Shi Y, *et al*. Akt activity determines sensitivity to mammalian target of rapamycin (MTOR) inhibitors by regulating cyclin D1 and C-myc expression. *J Biol* 2004;279:2737–46.
44. Wang Y, Mikhailova M, Bose S, Pan CX, deVere White RW, Ghosh PM. Regulation of androgen receptor transcriptional activity by rapamycin in prostate cancer cell proliferation and survival. *Oncogene* 2008;27:7106–17.
45. Yoshimoto M, Cunha IW, Coudry RA, *et al*. FISH analysis of 107 prostate cancers shows that *PTEN* genomic deletion is associated with poor clinical outcome. *Br J Cancer* 2007;97:678–85.
46. Higano CS, Alumkal JJ, Ryan CJ, *et al*. A phase II study of cixutumumab (IMC-A12), a monoclonal antibody (MAb) against the insulin-like growth factor I receptor (IGF-IR), monotherapy in metastatic castration resistant prostate cancer (mCRPC): feasibility of every 3-week dosing and updated results [abstract 189]. *Proc Am Soc Clin Oncol Genitourin Cancer Symp* 2010;:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=73&abstractID=30567; cited June 8, 2010]
47. Amato RJ, Jac J, Mohammad T, Saxena S. Pilot study of rapamycin in patients with hormone-refractory prostate cancer. *Clin Genitourin Cancer* 2008;6:97–102.
48. Nelson JB, Hedican SP, George DJ, *et al*. Identification of endothelin-1 in the pathophysiology of metastatic adenocarcinoma of the prostate. *Nat Med* 1995;1:944–9.
49. Carducci MA, Padley RJ, Breul J, *et al*. Effect of endothelin-A receptor blockade with atrasentan on tumor progression in men with hormone-refractory prostate cancer: a randomized, phase II, placebo-controlled trial. *J Clin Oncol* 2003;21:679–89.
50. Carducci MA, Saad F, Abrahamsson PA, *et al*. A phase 3 randomized controlled trial of the efficacy and safety of atrasentan in men with metastatic hormone-refractory prostate cancer. *Cancer* 2007;110:1959–66.
51. Nelson JB, Love W, Chin JL, *et al*. Phase 3, randomized, controlled trial of atrasentan in patients with non-metastatic, hormone-refractory prostate cancer. *Cancer* 2008;113:2478–87.
52. Armstrong AJ, Creel P, Turnbull J, *et al*. A phase I–II study of docetaxel and atrasentan in men with castration-resistant metastatic prostate cancer. *Clin Cancer Res* 2008;14:6270–6.
53. James ND, Caty A, Borre M, *et al*. Safety and efficacy of the specific endothelin-A receptor antagonist ZD4054 in patients with hormone-resistant prostate cancer and bone metastases who were pain free or mildly symptomatic: a double-blind, placebo-controlled, randomised, phase 2 trial. *Eur Urol* 2008:55:1112–23.
54. Small EJ, Fratesi P, Reese DM, *et al*. Immunotherapy of hormone-refractory prostate cancer with antigen-loaded dendritic cells. *J Clin Oncol* 2000;18:3894–903.
55. Small EJ, Schellhammer PF, Higano CS, *et al*. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. *J Clin Oncol* 2006;24:30–94.
56. Higano CS, Schellhammer PF, Small EJ, *et al*. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. *Cancer* 2009;115:3670–9.
57. Kantoff P, Higano CS, Berger ER, *et al*. Updated survival results of the IMPACT trial of sipuleucel-T for metastatic castration-resistant prostate cancer (CRPC) [abstract 8]. *Proc Am Soc Clin Oncol Genitourin Cancer Symp* 2010;:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=73&abstractID=30778; cited June 8, 2010]
58. Higano CS, Corman JM, Smith DC, *et al*. Phase 1/2 dose-escalation study of a GM-CSF–secreting, allogeneic, cellular immunotherapy for metastatic hormone-refractory prostate cancer. *Cancer* 2008;113:975–84.

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