# New drugs in prostate cancer

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**Purpose of review**

The survival of hormone-refractory metastatic prostate cancer patients has improved with the use of docetaxel-based chemotherapy. The survival benefits, however, are modest suggesting that rationally designed therapeutic approaches are needed. We discuss recent developments in the therapeutic approach to advanced metastatic hormone-refractory prostate cancer, including molecularly targeted therapy, signal transduction inhibitors, stem-cell targeted therapy, anti-angiogenic compounds, vaccines and immunomodulating agents, differentiation agents, cytotoxics, and pro-apoptotic agents.

**Recent findings**

Over 200 compounds have entered clinical development for use in advanced prostate cancer, alone or in combination with cytotoxic agents such as docetaxel, or in other combinations. This article will review the results of emerging targets since the approval of docetaxel in 2004, concentrating on some of those compounds that, in our opinion, have the greatest potential and rationale for use.

**Summary**

The growing field of targeted molecular therapy of prostate cancer has opened up numerous opportunities for therapeutic impact. Knowledge of the molecular determinants of progression, relapse after local therapy, chemotherapeutic resistance, and hormone refractoriness remains essential in the rational design of clinical trials of these agents. Given the complexity, heterogeneity, and crosstalk of molecular pathways and the molecular lesions in prostate cancer, combination or sequential therapy may be a necessary step towards significant therapeutic progress. Novel translational clinical trial methodologies may assist in a more rapid identification of active compounds at biologically active doses for phase-III testing.

**Keywords**

angiogenesis, apoptosis, hormone refractory, metastatic prostate cancer, novel agents, prostate cancer, targeted therapy

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**Abbreviations**

| | |
|---|---|
| **EGFR** | epidermal growth factor receptor |
| **HRPC** | hormone-refractory prostate cancer |
| **PDGFR** | platelet-derived growth factor receptor |
| **PSA** | prostate-specific antigen |
| **VEGF** | vascular endothelial growth factor |


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## Introduction

In 2004, docetaxel (Taxotere, Sanofi-Aventis, Bridgewater, NJ) with prednisone was US Food and Drug Administration (FDA) approved for the treatment of metastatic, progressive, hormone-refractory prostate cancer based on findings from TAX327 and SWOG 9916 [1••,2]. Survival was increased in TAX327 by a median of 2.5 months from 17.4 to 18.9 months as compared with mitoxantrone and prednisone, the previous standard of care, and was similar to results seen with docetaxel and estramustine in SWOG 9916. Importantly, quality-of-life and pain measures were improved despite the higher risk for severe neutropenia, fatigue, alopecia, diarrhea, stomatitis, nail changes, tearing, peripheral edema, and neuropathy. While docetaxel represents an improvement in care and the first demonstrable survival advantage in this patient population, treatment remains palliative and survival benefits are modest. The identification of molecular lesions that reproduce the aggressive cancer phenotype, which are not present in normal tissues, is essential to further the field beyond the current cytotoxic plateau and to move towards the development of targeted novel agents.

## Growth factor and signal transduction pathways

The last decade has witnessed the identification of hundreds of cell-signaling molecules important in the development of prostate cancer. Crosstalk between hormonal and growth factor signaling pathways creates a redundancy and complexity to drug development efforts [3]. Abnormal expression of a target protein may be insufficient as a surrogate marker for a therapeutic target, without independent validation of that target's role in reproducing the cancer phenotype and in mediating the response to a drug [4]. Indeed, the androgen receptor represents the most valid target to date in prostate cancer, and novel strategies to more potently target the androgen axis are in development [5••]. Unfortunately, it is often the expensive failure of a certain drug class to

impact response, time-to-progression, or survival in prostate cancer that triggers a reconsideration of the underlying biological model for a known potential target. Table 1 provides an overview of the most advanced novel agents in clinical trials in prostate cancer.

In metastatic hormone-refractory prostate cancer (HRPC), several classes of agents that modify growth factor pathways hold some promise and are in early phase trials. These include rapamycin analogs that target the Akt/PI3 kinase/mTOR pathway, monoclonal antibodies, and inhibitors of upstream growth factor receptors such as HER-2/3, IGF-R, IL-6R, and platelet-derived growth factor receptor (PDGFR). PTEN is a tumor suppressor that is lost in a majority of metastatic prostate cancers, leading to unrestrained activation of the Akt/PI3 kinase pathway and autonomous growth and survival [6,7]. Akt activation and/or PTEN loss have been linked to hormonal resistance, chemotherapeutic insensitivity, biologically aggressive behavior, high Gleason sum, and relapse after local therapy [8,9]. Mouse models of PTEN loss or Akt activation have demonstrated growth inhibition, restoration of chemosensitivity, and improved time-to-progression with inhibitors of this pathway, including rapamycin analogs [10–12]. Mechanistic dose-finding pre-prostatectomy studies are in progress in prostate cancer with three rapamycin analogs: CCI-779 (Temsirolimus, Wyeth, Collegeville, PA), RAD001 (Everolimus, Novartis, Cambridge, MA), and rapamycin itself [13–16]. The development of these agents will be dependent on the establishment of surrogate markers of biologic effect, the identification of subgroups of responders, and drug characteristics such as dose, pharmacokinetic variability, and tolerability. Everolimus, in combination with the upstream epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib, is in phase-II development and the Ariad agent AP23573 (Cambridge, MA) is being evaluated currently as a single agent in metastatic HRPC. All agents in this class have a well described pattern of toxicity, including stomatitis, acneform rash, glucose intolerance, nausea, fatigue, mild thrombocytopenia, arthralgias, electrolyte abnormalities, and possibly increased risks of infection [17]. Their long-term immunosuppressive safety in prostate cancer patients has yet to be tested, but they have been evaluated favorably in renal cell carcinoma and other tumor types [18•]. The use of these agents in combination with docetaxel is under investigation and requires careful monitoring owing to metabolic and myelosuppressive interactions. As these agents are primarily cytostatic in prostate cancer, combination therapy with other biologic agents will likely be necessary.

While agents targeting the EGFRs such as gefitinib and trastuzumab have not been successful in metastatic prostate cancer, it is likely that the EGFR and HER-2 targets for these drugs may not be causal in prostate cancer [19–21]. Indeed, HER-2 overexpression in prostate cancer is rare, unlike the case in subsets of breast cancer [21]. Recent studies, however, may point to other growth factors and paracrine signals that may be of greater importance, such as HER-3, IGF-R, and cytokine receptors, such as the receptors for TGF-β and IL-6. Mellinghoff *et al.* [22•] found that HER-2/HER-3 dimerization and activation led to optimization of androgen-receptor signaling in the setting of androgen depletion, pointing to a potential novel therapeutic target. The ligand for HER-3 is neuregulin, and potential therapeutic agents that may target HER-2/HER-3 signaling include the monoclonal antibody pertuzumab (Omnitarg, Genentech, San Francisco, CA) and the intracellular inhibitor lapatinib (GlaxoSmithKline, Philadelphia, PA) [23,24].

The endothelin axis has been proposed as an important mediator of the bone–prostate cancer interface and paracrine signaling target. Endothelin receptors are overexpressed in metastatic HRPC and higher levels of

**Table 1 Selected novel agents in phase-II/III development in metastatic hormone-refractory prostate cancer**

| Target | Agent, sponsor | Phase | Brief eligibility overview |
|---|---|---|---|
| Vitamin D receptor | Calcitriol (DN101), Novacea | III | ASCENT II: docetaxel ± DN101 in metastatic HRPC |
| Endothelin axis | Atrasentan (Xinlay), SWOG | III | Docetaxel ± atrasentan in metastatic HRPC |
| Vascular endothelial growth factor | Bevacizumab (Avastin), CALGB | III | CALGB 90401: docetaxel ± bevacizumab in metastatic HRPC, first line |
| Vaccine strategies | Prostate GVAX (Cell Genesys), Provenge (Dendreon), TRICOM (NCI, ECOG) | III | GVAX (VITAL-1), Provenge (D9902B) – first-line metastatic, asymptomatic HRPC VITAL-2: docetaxel ± GVAX in symptomatic HRPC |
| Epidermal growth factor receptor (HER-2/HER-3) | Lapatinib, ECOG | II | Rising PSA setting (nonmetastatic) |
| PTEN/Akt and mTOR pathway | Temsirolimus (Wyeth), Everolimus (Novartis), Rapamycin (Johns Hopkins), AP23573 (Ariad) | I–II | Preoperative pharmacodynamic and dose-finding studies; combination with docetaxel in metastatic HRPC (Dana Farber and MSKCC) |

HRPC, hormone-refractory prostate cancer.

endothelin correlate with progressive disease [25]. While endothelin is a potent vasoconstrictive agent, it may also regulate cellular mitogenic pathways in prostate cancer and osteoblasts, and may play a role in the mediation of bone-related pain from metastatic prostate cancer. Atrasentan (Xinlay, Abbott Labs, Abbott Park, IL) has been developed as highly selective ET-A receptor antagonist and is the most clinically developed agent of this class in prostate cancer [26]. In the phase-III trial, 809 patients with metastatic HRPC were randomized to placebo or 10 mg of oral atrasentan, with the primary clinical endpoint being time to progression (TTP) [27]. Although TTP was not found to be statistically significantly different from placebo in the intent-to-treat analysis, several secondary endpoints indicated clinical activity, including improvements in quality-of-life scores, pain scores, and reductions in the rise of laboratory markers including alkaline phosphatase and prostate-specific antigen (PSA). While atrasentan was not approvable on the basis of these data and out of concerns for cardiovascular toxicity, these results clearly point to biologic activity of the endothelin axis in modulating osteoblastic metastases, and underscore the importance of trial design in this population. Further development of this agent in combination with docetaxel or in select bone-only subgroups of patients may continue. Another ET-A receptor antagonist, ZD4054 (Astra Zeneca, Waltham MA), is also in phase-II development at this time [28].

Prostate cancer cells express high levels of platelet-derived growth factor receptor (PDGFR), and this signaling pathway utilizes the PI3 kinase/Akt pathway, which has been implicated in prostate cancer progression [29]. A phase-I study of imatinib (Gleevec, Novartis, Cambridge, MA) a small-molecule PDGFR tyrosine kinase inhibitor used to treat chronic myeloid leukemia and gastrointestinal stromal tumor, has been conducted in advanced prostate cancer alone and in combination with weekly docetaxel. The combination of imatinib 600 mg and docetaxel 30 mg/m$^2$ weekly for four out of six weeks demonstrated a more than 50% PSA reduction in eight of 21 patients (38%), with several durable (>18 month) responses [29]. A second-line randomized trial of this combination sponsored by the National Cancer Institute Prostate Cancer SPORE clinical consortium is underway.

## Prostate cancer stem-cell targeted therapy

While a true prostate cancer stem-cell phenotype has yet to be identified, several molecular stem-cell targets overexpressed in prostate cancer have been described and include elements of the hedgehog signaling pathway, human telomerase, and CD133 [30•,31–33]. Targeting the hedgehog embryonic pathway, which is overexpressed in many metastatic prostate cancers, has been shown to prevent prostate regeneration after androgen withdrawal and to lead to prolonged responses in PC-3 xenograft models [30•]. Novel cyclopamine analogs, which inhibit a downstream hedgehog signal, are in preclinical development.

Human telomerase is responsible for the maintenance of chromosome stability and length during cell division, and is overexpressed in nearly all cancers. In prostate cancer, telomerase may be regulated by androgen or growth factors, and is overexpressed as compared with normal and benign prostatic hypertrophy tissue [31,32]. Strategies targeting telomerase have been reviewed in detail by Biroccio and Leonetti [31]. Other markers of basal epithelial prostate cells that may indicate a subset of cancers derived from putative prostate stem cells include lack of androgen receptor, CD133, $\alpha_2\beta_1$ integrin overexpression, Bcl-2, TGF-β signaling, high-molecular-weight cytokeratins, hepsin, and potentially TMPRSS2-ETS fusion proteins [30•,31–33,34••,35,36]. The identification of clonogenic populations of cells in prostate cancer with the ability to self-renew and differentiate would allow the testing of novel agents directed at these cells, provided there was tolerability to normal stem-cell populations.

## Anti-angiogenic agents

Prostate cancer is known to overexpress vascular endothelial growth factor (VEGF) and its receptors, and VEGF levels correlate with disease stage and perhaps survival in the metastatic setting, with levels falling after surgical resection of primary tumors [37,38]. The mechanism of action of anti-VEGF therapies is unclear, and potentially includes a normalization of vasculature for facilitated delivery of chemotherapy, a decrease in oncotic interstitial pressure from leaky capillary membranes, improved recruitment of mature dendritic cells and immunostimulation, and true antineovascularization effects [39–42]. A phase-III study CALGB 90401 that will randomize patients in a phase-III trial to docetaxel compared with docetaxel and bevacizumab (Avastin, Genentech, San Francisco, CA), including prednisone in each arm, is now open with a goal accrual of 1020 patients over 3 years. This follows on the heels of a large phase-II study, which demonstrated the safety and efficacy of docetaxel, estramustine, and bevacizumab in combination for HRPC [43].

Additional agents with anti-angiogenic properties include thalidomide and its analogs, Revlimid and Actimid (Celgene, Summitt, NJ), as well as small-molecule inhibitors of the VEGF receptor tyrosine kinase such as Sorafenib (Onyx, Emeryville CA and Bayer, West Haven CT) and Sutent (SU11248, Pfizer, Cambridge, MA) [44–46]. These agents are in phase-II development

in HRPC. Thalidomide analogs likely have multiple mechanisms of action, including inhibition of VEGF as well as improved T-cell costimulatory function, TNF-α inhibition, and a decrease in IL-6 levels [44,45]. A phase-II randomized study of thalidomide and docetaxel in HRPC demonstrated impressive PSA declines, TTP, and overall survival but was complicated by a high rate of thrombosis, sedation, and neuropathy in the experimental arm, necessitating the introduction of therapeutic low-molecular-weight heparin prophylaxis [47]. Novel thalidomide analogs are in phase-II development in prostate cancer, and are expected to have a lower incidence of vascular and neurotoxic adverse events [48]. The high potency of these agents in terms of T-cell stimulation, anti-angiogenic properties, and oral availability make them attractive as therapeutic agents.

## Immunologic approaches

Several vaccination strategies have progressed beyond phase-II testing in prostate cancer, including Provenge, a PAP-activated dendritic-cell-based vaccine, and Prostate GVAX, a whole-cell allogeneic vaccine. Both of these agents are under evaluation in the phase-III setting [49•]. Provenge (Sipuleucel-T, Dendreon, San Francisco, CA) is a proprietary process of antigen delivery to activated antigen-presenting cells, collected from patients through leukapheresis, stimulated with fusion PAP-GMCSF protein, and reinjected intradermally every 4 weeks [50]. Initial results from small phase-III studies (D9901 and D9902A) involving a total of 225 patients with asymptomatic metastatic HRPC did not significantly demonstrate improved time to disease or pain progression, the primary endpoints [51]. While not originally powered to detect a survival benefit, overall survival was improved by an average of 4 months in each study. Analyses based on chance imbalances in prognostic factors and use of chemotherapy after vaccination did not seem to reduce this survival finding. Dendreon is submitting a Biologics License Application to the FDA for marketing approval.

Prostate GVAX (Cell Genesys, San Francisco, CA) is a form of active immunotherapy using whole-cell allogeneic prostate cell lines (PC-3 and LnCaP) virally transduced to express an immune adjuvant GM-CSF, lethally irradiated, and injected intradermally. Given that GM-CSF likely facilitates the maturation and activation of dendritic cells, initial work extrapolated early melanoma studies to mouse models of prostate cancer with results showing prolonged survival and tumor regression [52,53]. A phase-II study of prostate GVAX was conducted in 34 patients with metastatic HRPC. Median survival in this trial was 26 months, historically very favorable, but again, observed in select, asymptomatic patients [54]. A further evaluation of 80 patients with metastatic HRPC treated at higher doses demonstrated one partial PSA response and improvement in markers of bone turnover, with survival analysis still ongoing [55]. A phase-II trial of GVAX compared with docetaxel (VITAL-1) in 600 men with minimally symptomatic metastatic HRPC is currently accruing patients, and a second phase-III study examining docetaxel and prednisone with or without GVAX has been initiated (VITAL-2).

Finally, two other vaccine approaches are in early testing and include the Prostvac-VF recombinant vaccinia–fowlpox PSA vaccine (TRICOM) and the BLP25 MUC1 liposomal vaccine MUC-1 [56,57]. The use of vaccines alone or in combination with chemotherapy or biologic agents, such as CTLA4 blocking antibodies, is an exciting area of preclinical and clinical development [58].

## Differentiation and apoptotic therapy

Two strategies to exploit the latent and resistant nature of tumor growth in prostate cancer are differentiation therapy and the use of agents that target the apoptotic machinery of cancer cells. In prostate cancer, epidemiologic data suggest that the vitamin D receptor is a potentially valid target, given the link of vitamin D deficiency with prostate cancer development, reviewed elsewhere [59]. *In vitro*, calcitriol may have growth inhibitory, proapoptotic, and differentiating properties in prostate cancer, as well as potential chemosensitizing properties, thus leading to a rationale for clinical trials [60,61]. Based on favorable phase-II results of calcitriol and docetaxel in combination, Beer *et al.* [62,63•] recently reported interim results from a phase-II randomized trial (ASCENT) of docetaxel and prednisone with or without DN-101 (Novacea, San Francisco, CA), a proprietary oral calcitriol analog. In this randomized multiinstitutional study of 250 men with progressive metastatic HRPC treated with weekly docetaxel with or without DN101, the primary endpoint was PSA response rate, a typical phase-II endpoint. With a median follow-up of 18.3 months, neither PSA nor clinical response endpoints were met (6-month PSA response 58% compared with 49%, $P = 0.07$, and measurable disease response rate 29% compared with 24%, $P = 0.58$ in the placebo compared with treated subjects, respectively). Despite being underpowered to detect a difference in survival, however, the estimated median survival was nonsignificantly prolonged, from 16.4 to 23.5 months [hazard ratio 0.70, 95% confidence interval (CI) 0.48–1.03, $P = 0.07$], and better tolerated than docetaxel alone [63•]. This difference became significant with a prespecified multivariate adjustment based on chance imbalances in this small sample size. A larger study

with typical phase-III survival endpoints is planned (ASCENT II) to confirm these findings.

Other differentiation strategies include inhibitors of histone deacetylase and DNA methyltransferase, enzymes responsible for the epigenetic silencing of gene expression. Histones maintain DNA in a closed, coiled configuration, and this activity is mediated by a reversible acetylation process, in which acetylation of lysine residues on select histone tails favors transcription. Aberrant hypermethylation and gene silencing of specific promoter regions in prostate cancer has been described, such as the antioxidant enzyme GST-II and the tumor suppressor p21 [64]. The rationale behind agents that target histone deacetylase or DNA methyltransferase is their ability to induce broad gene re-expression in preclinical models of prostate cancer, which may induce apoptosis, upregulate p21 signaling, and arrest growth [65•]. Phase-II studies are planned using SAHA (Merck, Whitehouse Station, NJ), an orally bioavailable histone deacetylase inhibitor, in metastatic HRPC. The development of these agents in prostate cancer will require careful attention to pharmacodynamic endpoints, toxicity, potential differentiating effects such as transient PSA rises, and the potential for interactions with chemotherapy and other biologic agents [66,67].

As the anti-apoptotic Bcl-2 protein is overexpressed in metastatic HRPC, and resistance to cell death seems to be dominant over proliferation in these tumors, pro-apoptotic strategies are attractive therapeutically [68]. The mechanism of Bcl-2 overexpression is unclear, however, and could be related to PTEN loss and/or Akt pathway activation, thus providing a common mechanism for the observed joint occurrences with tumor progression [69•,70]. Two agents that have progressed to the phase-II setting include the antisense Bcl-2 molecule oblimersen sodium (Genasense, Berkeley Heights, NJ) and the proteasome inhibitor bortezomib (Velcade, Millenium Pharmaceuticals, Cambridge, MA) [71,72]. Current results have demonstrated feasibility and safety but unclear efficacy or target validation in prostate cancer.

## Novel cytotoxics

The dose limitations of docetaxel therapy in metastatic HRPC are predominantly those of peripheral neurotoxicity and myelotoxicity, and the search for well tolerated novel cytotoxic compounds continues, both in the front line and in the second-line setting. One agent in development for second-line therapy is satraplatin (Spectrum Pharmaceuticals, Irvine, CA), a novel oral platinum analog that may fulfill a niche in second-line therapy if it is well tolerated and shown to improve survival over corticosteroids in the ongoing SPARC phase-III trial [73]. The epothilones are a class of microtubule targeting cytotoxic agents in development for second-line and relapsed HRPC. While sharing a common mechanism of action with the taxanes, they are not apparently susceptible to P-glycoprotein induced drug efflux [74]. The epothilone-B analog BMS-247550 (Ixabepilone, Ingenta, Cambridge, MA) has been studied in a phase-II trial of men with HRPC [75]. Initial results demonstrated comparable PSA declines and progression-free survival to that seen with docetaxel-based therapy. Use of these drugs may be limited by dose-limiting neurotoxicity similar to that seen with the taxanes. The use of BMS-247550 in taxane-resistant HRPC is being investigated currently in the second-line setting as compared with mitoxantrone and prednisone, and has shown similar PSA declines of about 20% [76]. Finally, monoclonal antibodies (mAbs) targeted to prostate cancer cells with tagged cytotoxic agents represent a novel approach to therapy. One agent, MLN2704 (Millenium Pharmaceuticals, Cambridge, MA), is a prostate-specific membrane antigen conjugated maytansinoid agent and is in phase-I/II trials currently in HRPC [77]. Radiopharmaceuticals tagged to mAbs have also shown some promise and are also in phase-II trials [78–81]. Table 2 provides an overview of second-line clinical trials that are ongoing in metastatic HRPC.

## Conclusion

Metastatic HRPC in 2006 remains an incurable disease with a median survival of 18–20 months with current docetaxel-based chemotherapy regimens. Patients that are asymptomatic or have slow PSA doubling times

**Table 2 Agents in phase-II/III trials for use in second-line therapy after docetaxel failure in metastatic hormone refractory prostate cancer**

| Agent | Phase | Trial, sponsor |
|---|---|---|
| Satraplatin | III | SPARC trial (Spectrum Pharmaceuticals): prednisone ± satraplatin |
| Epothilone B Analog BMS-247550 (Ixabepilone) | II | ECOG: BMS compared with mitoxantrone and prednisone |
| Targeted cytotoxics and radiopharmaceuticals: MLN2704, $^{177}$Lu/ $^{90}$Y J591, | II | MLN2704: MSKCC, Millenium Pharmaceuticals; J591: Cornell University |
| PDGFR: Imatinib(Gleevec) | II | MD Anderson and Prostate Cancer Foundation with docetaxel |

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