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Overcoming Chemotherapy Resistance in Prostate Cancer

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Abstract

Although treatment for prostate cancer has improved over the past several years, taxanes remain the only form of chemotherapy that improves survival in patients with metastatic castration-resistant prostate cancer (mCRPC). In addition to the promising therapeutic cancer vaccines and newly developed agents targeting androgen receptor signaling, chemotherapy-based treatments will likely continue to play a significant role in patients with mCRPC. Recently published data that showed that a second taxane (cabazitaxel) extends survival after progression on docetaxel was a significant step forward, but also highlighted the need to overcome taxane resistance in prostate cancer. Preliminary evidence suggests that several treatment strategies may improve the activity of taxanes in prostate cancer and perhaps enhance clinical outcomes.

Introduction

The demonstration that docetaxel in combination with prednisone (or estramustine) could improve overall survival (OS) in men with castration-resistant metastatic prostate cancer (mCRPC) immediately generated 2 questions: How can taxane-based therapy be improved? Can the patients who develop progression postdocetaxel be successfully treated with alternative agents? Though the first question has yet to be definitively answered, 2 trials presented in 2010 (with cabazitaxel and abiraterone) have presented alternative successful strategies on treating patients whose disease progresses on docetaxel.

As aspects of this question have evolved during the last decade, so has our understanding of prostate cancer. Additional investigations from taxane combinations, novel taxanes, and emerging data about intermittent scheduling provide the basis for future strategies. Clinical data from several trials have suggested that the androgen receptor (AR) remains a viable target, even in patients whose disease has progressed on chemotherapy. Furthermore, AR signaling may be one mechanism driving resistance to a variety of agents, including taxanes.

Taken together, these new insights have led to new strategies for treating the prostate cancer patient resistant to docetaxel.

Mechanisms of Taxane Activity and Resistance

As prostate cancer progresses, heterogeneity increases and multiple mechanisms may account for the drug resistance, even in the same patient. Taxanes exert an antineoplastic effect by stabilizing microtubules, which are fibrillar components of the intracellular apparatus that play a vital role in migration, intracellular transport, signaling, and proliferation. Microtubules are composed of α - and β -tubulin and exist in a dynamic equilibrium with free intracellular α - and β -tubulin subunits. Microtubule elongation, which occurs through the addition of α - and β -tubulin subunits to existing microtubules, is essential to the role of microtubules in mitosis (1). Taxanes can bind to tubulin, preventing the assembly of microtubules, as well as microtubular depolymerization. For cancer cells undergoing rapid proliferation, effects on microtubules ultimately lead to cell cycle arrest in metaphase, followed by apoptosis (2). Specifically for prostate cancer cells, taxane-impaired microtubule function may lead to decreased AR nuclear translocation. Resistance to taxanes may or may not involve alternative AR signaling pathways. The lower activity of modern hormonal therapies, such as MDV3100 and abiraterone, observed post-taxane treatments might be due to taxane-induced AR signaling changes. Alternatively, it simply might be due to higher burdens of disease in the post-taxane treatment-treated patient population.

General mechanisms of taxane resistance have been widely investigated (Table 1). Cancer cells with multidrug resistance (*mdr1*) gene expression may be able to minimize the intracellular concentration of taxanes by increasing efflux through a P-glycoprotein pump (3). In addition, modulation of microtubule characteristics may alter responsiveness to taxanes. For example, increased dynamic activity of the microtubules after treatment can decrease the efficacy of taxanes (4, 5). Mutations leading alterations in the microtubule-binding site of taxanes or in microtubule-associated proteins can also reduce the efficacy of taxanes (6, 7). One particular mechanism of resistance, overexpression of the $\beta 111$ isoform of tubulin, maybe particularly important in prostate cancer, in which βIII overexpression has been associated with castration-resistant disease and the decreased efficacy of docetaxel (8, 9).

AR signaling drives prostate cancer cellular proliferation, even in disease considered castration resistant (10). As prostate cancer progresses, molecular mechanisms such as AR splice variants could develop, which could enhance ligand-independent AR signaling and lead to drug resistance. Increased AR expression, through either amplified gene expression or increased molecular stability, may allow the cells to become increasingly androgen sensitive (11, 12). Enhanced efficacy of nuclear steroid receptors that function downstream from the AR and serve as coactivators for transcription factors may also promote chemotherapy resistance (13). In addition, prostate cancer cells may develop autocrine- or paracrine-mediated cellular growth, producing various androgens to drive these aberrant mechanisms through cytochrome P17 (CYP17)-mediated androgen synthesis (14, 15).

AR signaling cascades have been associated with cellular proliferation pathways and decreased apoptosis (16). In addition, AR signaling has been shown to regulate interactions with the tumor microenvironment, via mediators such as VEGF and transforming growth factor- β , promoting cellular proliferation (17, 18). It is possible that altered androgen signaling cascades, through these oncogenic processes, can lead to chemotherapy resistance in patients being treated with taxanes.

Cabazitaxel Preclinical Data

Cabazitaxel bears structural and mechanistic similarity to docetaxel (Fig. 1; refs. 19–22). Nonetheless, available preclinical data suggest the ability to overcome first-generation taxane resistance. The first *in vitro* assessment of cabazitaxel was reported approximately a decade ago, with antitumor activity noted in breast carcinoma, cervical adenocarcinoma, and leukemia cell lines at nanomolar concentrations (23). The activity of the agent was clearly present in cell lines resistant to standard cytotoxic agents, including the taxanes docetaxel and paclitaxel, perhaps mediated by a lower affinity for the P-glycoprotein efflux pump (24). Subsequent *in vivo* assessment in colon C38 and pancreas P03 murine tumor xenografts showed nearly complete tumor regression (25). In the hormone-resistant DU 145 prostate cancer cell line, complete tumor regression and prolonged survival were observed.

After confirmation of antitumor activity using *in vitro* and *in vivo* models, including the models resistant to other taxanes, subsequent efforts focused on eliciting the pharmacokinetic profile of the agent. In early animal studies, the agent exhibited an atypical distribution. ^{14}C -labeled cabazitaxel was administered to mice at increasing doses, with a proportional increase in plasma concentration (26). In contrast, central nervous system (CNS) concentrations of the agent increased more than proportionally. In rodent models, CNS accumulation of the drug increased when plasma concentrations were greater than 11 $\mu\text{mol/L}$, suggesting that P-glycoprotein transport could exhibit saturable kinetics (27). In orthotopic murine models incorporating human glioblastoma cell lines, significant tumor regression with cabazitaxel therapy has been observed (28). Whether drug transporters are mechanistically linked to overcoming taxane resistance with cabazitaxel is not yet clear.

Cabazitaxel Phase I Data

The above encouraging preclinical data led to a phase I trial of cabazitaxel, including 25 patients with advanced solid tumors resistant to prior chemotherapy administration (24). The median age of the study population was 60, and the majority had either prostate or colorectal cancer ($n = 8$ for both). Approximately 32% of patients had received prior taxane therapy. The rate of dose-limiting toxicity (DLT) exceeded predefined limits at a dose of 25 mg/m^2 , including protracted grade 4 neutropenia in 2 patients and febrile neutropenia in a separate patient. Therefore, 20 mg/m^2 emerged as the recommended phase II dose, with 9 patients treated at this dose level with no associated DLTs. In this phase I experience, antitumor activity was noted in 2 prostate cancer patients treated at 15 and 2.5 mg/m^2 , respectively. Both experienced a PSA decline greater than 50%, and a reduction in target lesions characterized as a partial response.

Phase III Testing of Cabazitaxel

The interesting results in advanced prostate cancer in the phase I trial, coupled with the provocative preclinical data, directly led to a phase III trial in mCRPC, in which patients were randomized to cabazitaxel and prednisone or mitoxantrone and prednisone (29). The entry criteria for the trial (termed TROPIC) included progression of disease despite prior docetaxel therapy. This was the first phase III trial specifically designed for this population. Initially, a minimum dose of docetaxel was not required, but the trial was amended to specifically state that all patients needed to have received at least 225 mg/m² of docetaxel prior to entry. This requirement was incorporated to ensure that enrolled patients would be enriched for taxane resistance. For those patients with measurable disease, progression by Response Evaluation Criteria In Solid Tumors (RECIST) criteria was required. For those patients with nonmeasurable disease, either the appearance of new lesions or 2 consecutive increases in PSA 1 week apart were required either during or after docetaxel treatments. Exclusion criteria included prior radiation to >40% of the bone marrow, known brain metastases, prior mitoxantrone, an ejection fraction of less than 50%, or a history of severe hypersensitivity to polysorbate 80-containing drugs.

The trial was conducted in 26 countries and was stratified for Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1 versus 2) and measurable disease (present versus absent). The primary endpoint was OS using an intent-to-treat analysis. Prespecified secondary endpoints included a composite progression-free survival (PFS), PSA response rate, and time to PSA progression; pain response rate and time to pain progression; and tumor (RECIST) response rate and time to tumor progression. The composite PFS endpoint was determined by the first event to occur among PSA progression, tumor progression, pain progression, or death. The trial was designed with a 90% power to detect a hazard ratio (HR) of 0.75 for OS with a 2-sided type I error of 0.05. The study was designed to enroll 720 patients, and final analysis was planned after 511 deaths.

Cabazitaxel was administered intravenously at a dose of 25 mg/m² every 3 weeks, mitoxantrone was also administered every 3 weeks at a dose of 12 mg/m². All patients received oral prednisone 10 mg/day. Unlike paclitaxel or docetaxel, premedications in the cabazitaxel group did not include oral corticosteroids. An antihistamine, corticosteroid, and H₂ antagonist were intravenously given 30 minutes before a 1-hour infusion of cabazitaxel. The trial enrolled a total of 755 patients between January 2007 and September 2009. The patient characteristics were well balanced, but several features were notable. Of the enrolled population, 92% had an ECOG performance status of 0 to 1. The percentage of low performance status patients was surprisingly low given the limited life expectancy of this population. Median PSAs were 129.5 and 143.9 in the mitoxantrone and cabazitaxel group, respectively. More than half of the patients (53.5%) had bidimensionally measurable disease, and approximately one fourth of patients had visceral metastases. This proportion of patients is unusually high for an mCRPC population and may reflect a combination of the proscribed entry criteria and advanced nature of their disease. Most patients received 1 prior docetaxel-containing regimen (approximately 70%), but nearly 30% received 2 or more chemotherapeutic regimens prior to trial entry. The median doses of prior docetaxel in the

mitoxantrone and cabazitaxel arms was 529 and 576 mg/m², respectively. The median time from prior docetaxel to progression was less than 1 month.

At the time of final analysis, the median follow-up was 13.7 months. We note that patients with disease progression postdocetaxel in prior trials have had a life expectancy of approximately 11 to 13 months (12,13). A total of 585 deaths had occurred, and only 15 patients were lost to follow-up. The median number of cabazitaxel cycles was 6, whereas the median number of mitoxantrone cycles was 4. The OS endpoint was readily met, favoring cabazitaxel over mitoxantrone, HR = 0.70 [95% confidence interval (CI), 0.59–0.83; P < 0.0001]. The median survival was 15.1 months in the cabazitaxel arm, compared with 12.7 months in the mitoxantrone arm (Fig. 2). This was the first time an OS benefit for second line chemotherapy in mCRPC was shown. Secondary endpoints, in general, favored the cabazitaxel arm. PFS using a composite endpoint was also increased: 2.8 months versus 1.4 months, HR 0.74 (95% CI, 0.64–0.86; P < 0.0001). The median time to PSA progression was 6.4 for cabazitaxel versus 3.1 months for mitoxantrone. Pain responses and pain progression were not distinct between the 2 arms. An analysis of subsets clearly suggests that cabazitaxel retains activity in the patients treated with the highest docetaxel doses prior to trial entry (Table 2). Though the exact explanation cannot be ascertained from clinical data, the implications are that those whose disease progresses after prolonged docetaxel pretreatments remain excellent candidates for cabazitaxel.

Toxicity, as expected, was similar to that experienced with other taxanes, though the febrile neutropenia rate (7.5%) and death within 30 days of the last infusion (5%). Most of the deaths were due to neutropenia and consequences. Grade 3 to 4 neutropenia was 82% in the cabazitaxel arm versus 58% in the mitoxantrone arm. Given this risk of myelosuppression associated with cabazitaxel therapy, newer trials are being designed to assess the activity of lower doses of cabazitaxel. It should be noted that in TAX327, 3% of patients treated with docetaxel developed febrile neutropenia, and 2 deaths were due to sepsis (of 332 patients; ref. 30); thus, suggesting that some of the ability of cabazitaxel to overcome taxane resistance may be due to increased dose intensity. The U.S. Food and Drug Administration (FDA) label has provided specific recommendations on the use of granulocyte colony stimulating factor, and prescribing physicians are urged to be familiar with these guidelines for both primary and secondary prophylaxis. Of note, a similar dose and schedule of mitoxantrone in the "upfront" mCRPC setting showed a 22% rate of grade 3 to 4 neutropenia (13). Differences may be attributable to the underlying patient population or the weekly collection of blood counts in the TROPIC trial. Other grade 3 to 4 toxicities in the cabazitaxel arm included diarrhea at 6%, grade 3 to 4 fatigue and/or asthenia at 5% each, grade 3 to 4 nausea and/or vomiting at 2%, hematuria at 2%, and abdominal pain at 2%. Neuropathy was surprisingly mild.

Strategies for Overcoming Taxane Resistance

Intermittent chemotherapy

Given that both of the FDA-approved chemotherapeutic agents that have shown a survival advantage in prostate cancer are taxanes, strategies are needed to overcome taxane resistance (Table 3; refs. 29, 30). One potential approach is intermittent treatment with a taxane, which

may serve 2 purposes. First, with less constant exposure to the drug, from a theoretical perspective, one is less likely to "select" for taxane-resistant cell populations and, thereby, potentially delay the development of taxane-refractory disease. Second, from a clinical perspective, breaks in therapy or "drug holidays" may improve the quality of life for patients, allowing them to recover from the cumulative toxicity of chemotherapy during these "drug holidays." Resolution of drug side effects may also allow taxane therapy to be prolonged, given evidence of clinical efficacy, which could also improve outcomes (31, 32).

This intermittent approach was prospectively evaluated in a study of 250 patients randomized to 36 mg/m² of docetaxel administered weekly with either high-dose calcitriol or placebo. The investigators established arbitrary guidelines requiring that patients have a PSA decline of >50% and a PSA <4 ng/mL to qualify for a drug holiday. Qualifying patients remained on a treatment break until objective evidence of disease progression or PSA increased by 50% to a value >2.0 ng/mL. Approximately 20% (*n* = 45) of patients met these rather strict criteria for intermittent therapy, regardless of which arm of the study they were randomized to. Furthermore, 90.9% of patients were responsive to docetaxel upon resumption of therapy. Response was measured as either a second decline of 50% (45.5% of patients on drug holiday) or PSA stabilization (45.5% of patients). At last reported follow-up, approximately 36% of the 36 patients who resumed therapy met the same holiday criteria and were able to undergo at least 1 more additional break from therapy. In evaluable patients, the first drug holiday lasted a median of 18 weeks, and the second lasted a median of 11 weeks (33).

Other trials employing intermittent docetaxel in combination with other antineoplastic agents, as well as less stringent criteria for allowing drug holidays, have reported similar findings (34, 35). The results from a phase II study at the National Cancer Institute involving docetaxel combined with antiangiogenesis agents reported a median OS of >28 months, which compares favorably to contemporary trials that did not employ an intermittent strategy (35, 36). These data suggest that prolonged chemotherapy facilitated by intermittent treatment holidays could result in increased clinical benefit and, ultimately, prolonged survival.

In light of these findings, investigators have considered building on this strategy by employing alternative therapies during the holiday period as a way of extending the break. Biologic therapies have been suggested as possible treatments during the break from chemotherapy, in order to give patients an opportunity to recover from toxicity (34, 37). Such agents could potentially include monoclonal antibodies or immunomodulatory agents, as well as therapeutic cancer vaccines and modern hormonal therapies, which have shown a survival advantage in metastatic prostate cancer (29, 38, 39). These therapies may have greater clinical benefit after initial docetaxel therapy has debulked the tumor or stabilized its growth. More focused testing of this hypothesis should be a clinical trial priority.

Chemotherapy combinations

Therapeutic combinations have also been employed to overcome taxane resistance in prostate cancer, although targeting the microtubule apparatus with multiple agents, such as docetaxel and estramustine, has not yielded improved outcomes (40). Targeting multiple

mechanisms of tumor-cell proliferation has been extensively investigated. One such combination in prostate cancer includes taxanes with platinum-based chemotherapies, whose DNA-alkylating properties are cytotoxic. Two small studies have shown modest benefits with the addition of carboplatin to docetaxel in patients whose disease progressed on docetaxel alone. About 20% of patients had delayed disease progression of approximately 3 to 6 months and 50% PSA declines (41, 42). For a subset of patients requiring continued taxane therapy, a combination of a taxane and platinum may be a valid approach; however, no level I evidence exists to support the use of platinum in this setting. A randomized phase III trial of prednisone versus satraplatin (an oral platinum agent) and prednisone in patients who progressed on chemotherapy showed no OS benefit for patients treated with satraplatin (43). Although multiple combination trials were planned, no large trials were ever completed after the failure of the definitive phase III study.

Angiogenesis plays a potentially critical role in prostate cancer; thus, angiogenesis inhibition has also been evaluated in the treatment of prostate cancer (44, 45). Although single agent studies in prostate cancer have indicated minimal clinical impact, a large phase III study was conducted on the basis of the rationale that targeting neovasculature and microtubules could enhance the clinical impact of docetaxel alone (46). The results of this study, however, indicated that despite delayed disease progression, the antiangiogenic agent bevacizumab in combination with docetaxel did not significantly prolong survival relative to docetaxel alone (36). Nonetheless, angiogenesis may be a viable target in combination with docetaxel therapy if angiogenesis suppression can be maximized, thereby potentially limiting the escape mechanisms that can develop with current angiogenesis inhibitors (47). A phase II trial has combined 2 antiangiogenic agents, bevacizumab and thalidomide, with docetaxel. The results of this study, which also employed flexible dosing including drug holidays, suggest that this approach may substantially improve outcomes while yielding manageable toxicities, which included neutropenia in all patients that was successfully mitigated with growth factor support. Compared with docetaxel and bevacizumab in the phase III trial, the combination of docetaxel, bevacizumab, and thalidomide yielded a greater percentage of major PSA responses (90% versus 69.5%) and prolonged median OS (28.2 versus 22.6 months; refs. 35, 36). Furthermore, anecdotal evidence from the docetaxel-bevacizumab-thalidomide regimen suggests that patients with progressive disease on docetaxel alone can subsequently respond to further treatment when angiogenesis inhibition is added, perhaps suggesting a way to resensitize progressive disease to taxanes (48). Although a randomized prospective study will be required to confirm these tantalizing findings, numerous ongoing studies of docetaxel with angiogenesis inhibition, among other targeted agents, are showing merit in prostate cancer (Table 4; refs. 42, 49–60).

Until recently, agents that targeted the AR were thought to have a limited role in the treatment of patients whose disease had progressed on docetaxel. But recent studies have improved our understanding of androgen signaling and dramatically altered that notion (61). Abiraterone targets the CYP17 enzyme, further limiting testosterone production in patients with prostate cancer beyond gonadotropin-releasing hormone agonists alone (62–64). In a phase III trial, this modern update of ketoconazole showed a survival advantage in patients who had progressive disease on docetaxel. As a result, abiraterone was approved by the FDA (29). Similarly, MDV3100, an AR antagonist (ARA) that is substantially more potent than

commonly used ARAs such as bicalutamide, has shown preliminary clinical evidence of efficacy in patients previously treated with docetaxel (65, 66).

Growing evidence of the pivotal role of androgen signaling in the postchemotherapy setting has renewed interest in combining taxane-based chemotherapy with modern hormonal agents in patients with metastatic disease. Such combinations have been previously evaluated, but in this new context, the findings may have greater significance. One study combined docetaxel with ketoconazole, a potent CYP3A4 and a first-generation CYP17 inhibitor, in 42 patients with mCRPC. This study allowed holidays from docetaxel, but gave patients the option of continuing ketoconazole during the breaks from chemotherapy. Median OS of chemotherapy-naïve patients ($n = 27$) in this study was 36.8 months. It is interesting to note, however, that patients who had previously progressing disease on docetaxel ($n = 15$) had a median survival of 10.3 months when docetaxel was reintroduced with ketoconazole (67). Although this was a small trial, the OS of taxane-naïve patients compares favorably with contemporary studies. These hypothesis-generating data suggest that concurrent CYP17 inhibition may prolong taxane sensitivity, perhaps by suppressing secondary androgen production, but may not be effective at salvaging taxane efficacy. These data also suggest that combining a taxane with a second-generation CYP17 inhibitor such as abiraterone, or with a modern hormonal agent such as MDV3100, may be more clinically beneficial than treatment with a taxane alone.

Promising phase I data have also indicated the safety of combining a bone-seeking radiopharmaceutical with docetaxel. Agents such as ^{153}Sm ethylenediaminetetramethylenephosphonate (^{153}Sm -EDTMP) are intravenously administered and preferentially deliver beta-emitting radiation to areas of newly remodeled bone, such as sites of osteoblastic bone metastases (57). ^{153}Sm -EDTMP has been shown to significantly reduce bone-related pain in patients with metastatic prostate cancer and is approved by the FDA for palliation (55, 68, 69). A phase I study endeavored to combine targeted radiation (^{153}Sm -EDTMP) to the bone metastasis microenvironment with systemic treatment in the form of docetaxel. In the 28 patients evaluated, the primary finding was that the combination was well tolerated and did not result in dose-limiting myelosuppression, a toxicity of both therapies. Furthermore, 58% of patients had a $\geq 50\%$ PSA decline, and similar proportions of patients had a $\geq 50\%$ PSA decline among those who were previously treated with a taxane ($n = 8$) or those who were considered taxane refractory ($n = 4$). The findings of this study indicate that radiopharmaceutical combinations with docetaxel warrant further investigation and may impact the chemosensitivity of the underlying disease. In addition, recent studies with a new radiopharmaceutical, radium-223, have indicated that this agent may have a preferred side-effect profile relative to ^{153}Sm -EDTMP (70, 71). A combination study of radium-223 and docetaxel is currently ongoing (72).

Conclusion

Despite the advent of multiple new treatment options in the last 2 years, the role of taxane-based therapy will continue to be evaluated for patients with mCRPC. It remains to be seen whether combinations of the newer agents with taxanes will improve survival, as opposed to multiple, successive, single-agent therapies. In addition, the optimal sequence of therapy will

be evaluated, including the potential of newer androgen-synthesis inhibitors to enhance or abrogate subsequent taxane activity. Furthermore, the role of emerging biomarkers has yet to be defined (73). Well-designed, prospective trials will provide valuable guidance on these issues. Multiple phase III trials are now in progress. OS is the most common endpoint, but we note that Prostate Cancer Working Group II criteria are increasingly being adopted (74). As additional drugs are approved that change survival, it will be very important to validate endpoints other than survival, particularly when drugs are studied earlier in the disease.

Although novel hormonal agents and immunologic-based therapies have shown improvements in survival, taxane-based therapy will continue to be a viable option for patients with metastatic castrate-resistant disease for the foreseeable future (75). Thus, strategies to enhance the efficacy of taxane-based treatments will continue to remain vital for patients with advanced disease.

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References

1. Gelfand VI, Bershadsky AD. Microtubule dynamics: mechanism, regulation, and function. *Annu Rev Cell Biol* 1991;7:93–116. [PubMed: 1809357]
2. Jordan MA, Toso RJ, Thrower D, Wilson L. Mechanism of mitotic block and inhibition of cell proliferation by taxol at low concentrations. *Proc Natl Acad Sci U S A* 1993;90:9552–6. [PubMed: 8105478]
3. Kartner N, Riordan JR, Ling V. Cell surface P-glycoprotein associated with multidrug resistance in mammalian cell lines. *Science* 1983;221:1285–8. [PubMed: 6137059]
4. Dumontet C, Sikic BI. Mechanisms of action of and resistance to antitubulin agents: microtubule dynamics, drug transport, and cell death. *J Clin Oncol* 1999;17:1061–70. [PubMed: 10071301]
5. Gonpalves A, Braguer D, Kamath K, Martello L, Briand C, Horwitz S, et al. Resistance to Taxol in lung cancer cells associated with increased microtubule dynamics. *Proc Natl Acad Sci USA* 2001;98:11737–42. [PubMed: 11562465]
6. Giannakakou P, Gussio R, Nogales E, Downing KH, Zaharevitz D, Bollbuck B, et al. A common pharmacophore for epothilone and taxanes: molecular basis for drug resistance conferred by tubulin mutations in human cancer cells. *Proc Natl Acad Sci USA* 2000;97:2904–9. [PubMed: 10688884]
7. Huzil JT, Chen K, Kurgan L, Tuszynski JA. The roles of beta-tubulin mutations and isotype expression in acquired drug resistance. *Cancer Inform* 2007;3:159–81. [PubMed: 19455242]
8. Terry S, Ploussard G, Allory Y, Nicolaiew N, Boissière-Michot F, Mailié P, et al. Increased expression of class III beta-tubulin in castration-resistant human prostate cancer. *Br J Cancer* 2009;101: 951–6. [PubMed: 19690549]

9. Ploussard G, Terry S, Maillé P, Allory Y, Sirab N, Kheuang L, et al. Class III beta-tubulin expression predicts prostate tumor aggressiveness and patient response to docetaxel-based chemotherapy. *Cancer Res* 2010;70:9253–64. [PubMed: 21045157]
10. Holzbeierlein J, Lai P, LaTulippe E, Smith A, Satagopan J, Zhang L, 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. [PubMed: 14695335]
11. Koivisto P, Kononen J, Palmberg C, Tammela T, Hyytinen E, Isola J, et al. Androgen receptor gene amplification: a possible molecular mechanism for androgen deprivation therapy failure in prostate cancer. *Cancer Res* 1997;57:314–9. [PubMed: 9000575]
12. Gregory CW, Johnson RT Jr, Mohler JL, French FS, Wilson EM. Androgen receptor stabilization in recurrent prostate cancer is associated with hypersensitivity to low androgen. *Cancer Res* 2001; 61:2892–8. [PubMed: 11306464]
13. Xu J, Wu RC, O'Malley BW. Normal and cancer-related functions of the p160 steroid receptor co-activator (SRC) family. *Nat Rev Cancer* 2009;9:615–30. [PubMed: 19701241]
14. Stanbrough M, Bubley GJ, Ross K, Golub TR, Rubin MA, Penning TM, et al. Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. *Cancer Res* 2006;66:2815–25. [PubMed: 16510604]
15. Montgomery RB, Mostaghel EA, Vessel la R, Hess DL, Kalhorn TF, Higano CS, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. *Cancer Res* 2008;68:4447–54. [PubMed: 18519708]
16. Zhu ML, Kyprianou N. Androgen receptor and growth factor signaling cross-talk in prostate cancer cells. *Endocr Relat Cancer* 2008;15: 841–9. [PubMed: 18667687]
17. Boddy JL, Fox SB, Han C, Campo L, Turley H, Kanga S, et al. The androgen receptor is significantly associated with vascular endothelial growth factor and hypoxia sensing via hypoxia-inducible factors HIF1 α , HIF-2 α , and the prolyl hydroxylases in human prostate cancer. *Clin Cancer Res* 2005; 11:7658–63. [PubMed: 16278385]
18. Zhu ML, Partin JV, Bruckheimer EM, Strup SE, Kyprianou N. TGF- β signaling and androgen receptor status determine apoptotic cross-talk in human prostate cancer cells. *Prostate* 2008;68:287–95. [PubMed: 18163430]
19. Caplow M, Zeeberg B. Dynamic properties of microtubules at steady state in the presence of taxol. *Eur J Biochem* 1982;127:319–24. [PubMed: 6128228]
20. Kumar N. Taxol-induced polymerization of purified tubulin. Mechanism of action. *J Biol Chem* 1981;256:10435–41. [PubMed: 6116707]
21. White JG, Rao GH. Effects of a microtubule stabilizing agent on the response of platelets to vincristine. *Blood* 1982;60:474–83. [PubMed: 6124288]
22. Pal SK, Twardowski P, Sartor O. Critical appraisal of cabazitaxel in the management of advanced prostate cancer. *Clin Interv Aging* 2010; 5:395–402. [PubMed: 21152241]
23. Bissery M-C, Bouchard H, Riou J, Vrignaud P, Combeau C, Bourzat JD. Preclinical evaluation of TXD258, a newtaxoid In Proceedings of the 91st Annual Meeting of the American Association for Cancer Research; 2000 4 1–5; San Francisco, CA. Philadelphia (PA): AACR; 2000 Abstract nr 1364.
24. Mita AC, Denis LJ, Rowinsky EK, Debono JS, Goetz AD, Ochoa L, et al. Phase I and pharmacokinetic study of XRP6258 (RPR 116258A), a novel taxane, administered as a 1 -hour infusion every 3 weeks in patients with advanced solid tumors. *Clin Cancer Res* 2009;15: 723–30. [PubMed: 19147780]
25. Vrignaud P, Lejeune P, Chaplin D, Lavelle F, Bissery M-C. In vivo efficacy of TXD258, a newtaxoid, against human tumor xenografts In: Proceedings of the 91 st Annual Meeting of the American Association for Cancer Research; 2000 4 1–5; San Francisco, CA. Philadelphia (PA): AACR; 2000 Abstract nr 1365.
26. Archimbaud Y, Gires P, Pellerin R, Nichele G, Poulet D. Pharmacokinetics of a newtaxoid, 14C-TXD258, in blood, plasma and brain of the mouse, rat and dog In Proceedings of the 91st Annual Meeting of the American Association for Cancer Research; 2000 4 1–5; San Francisco, CA. Philadelphia (PA): AACR; 2000 Abstract nr 1375.

27. Cisternino S, Bourasset F, Archimbaud Y, Semiond D, Sanderink G, Scherrmann JM. Nonlinear accumulation in the brain of the newtaxoid TXD258 following saturation of P-glycoprotein at the blood-brain barrier in mice and rats. *Br J Pharmacol* 2003;138:1367–75. [PubMed: 12711638]
28. Dykes D, Sarsat J, Bissery M-C. Efficacy evaluation of TXD258, a taxoid compound against orthotopic and subcutaneous glioblastomas In Proceedings of the 91st Annual Meeting of the American Association for Cancer Research; 2000 4 1–5; San Francisco, CA. Philadelphia (PA): AACR; 2000 Abstract nr 1916.
29. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010;376:1147–54. [PubMed: 20888992]
30. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502–12. [PubMed: 15470213]
31. Beer TM, Garzotto M, Henner WD, Eilers KM, Wersinger EM. Intermittent chemotherapy in metastatic androgen-independent prostate cancer. *Br J Cancer* 2003;89:968–70. [PubMed: 12966410]
32. Beer TM, Garzotto M, Henner WD, Eilers KM, Wersinger EM. Multiple cycles of intermittent chemotherapy in metastatic androgen-independent prostate cancer. *Br J Cancer* 2004;91:1425–7. [PubMed: 15467765]
33. Beer TM, Ryan CW, Venner PM, Petrylak DP, Chatta GS, Ruether JD, et al. ASCENT(AIPC Study of Calcitriol ENhancing Taxotere) Investigators. Intermittent chemotherapy in patients with metastatic androgen-independent prostate cancer: results from ASCENT, a doubleblinded, randomized comparison of high-dose calcitriol plus docetaxel with placebo plus docetaxel. *Cancer* 2008;112:326–30. [PubMed: 17960793]
34. Bellmunt J, Albiol S, Albanell J. Intermittent chemotherapy in metastatic androgen-independent prostate cancer. *BJU Int* 2007;100: 490–2. [PubMed: 17669140]
35. Ning YM, Gulley JL, Arlen PM, Woo S, Steinberg SM, Wright JJ, et al. Phase II trial of bevacizumab, thalidomide, docetaxel, and prednisone in patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 2010;28:2070–6. [PubMed: 20308663]
36. Kelly WK, Halabi S, Carducci MA, George DJ, Mahoney JF, Stadler WM, et al. 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: Survival results of CALGB 90401. *J Clin Oncol* 28:LBA4511.
37. Lin AM, Ryan CJ, Small EJ. Intermittent chemotherapy for metastatic hormone refractory prostate cancer. *Crit Rev Oncol Hematol* 2007;61:243–54. [PubMed: 17161610]
38. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363: 411–22. [PubMed: 20818862]
39. Gulley JL, Arlen PM, Madan RA, Tsang KY, Pazdur MP, Skarupa L, et al. Immunologic and prognostic factors associated with overall survival employing a poxviral-based PSA vaccine in metastatic castrate-resistant prostate cancer. *Cancer Immunol Immunother* 2010;59:663–74. [PubMed: 19890632]
40. Machiels JP, Mazzeo F, Clausse M, Filleul B, Marcelis L, Honhon B, et al. Prospective randomized study comparing docetaxel, estramustine, and prednisone with docetaxel and prednisone in metastatic hormone-refractory prostate cancer. *J Clin Oncol* 2008;26: 5261–8. [PubMed: 18794543]
41. Regan MM, O'Donnell EK, Kelly WK, Halabi S, Berry W, Urakami S, et al. Efficacy of carboplatin-taxane combinations in the management of castration-resistant prostate cancer: a pooled analysis of seven prospective clinical trials. *Ann Oncol* 2010;21:312–8. [PubMed: 19633053]
42. Nakabayashi M, Sartor O, Jacobus S, Regan MM, McKearn D, Ross RW, et al. Response to docetaxel/carboplatin-based chemotherapy as first- and second-line therapy in patients with metastatic hormone-refractory prostate cancer. *BJU Int* 2008;101:308–12. [PubMed: 18184327]

43. Sternberg CN, Petrylak DP, Sartor O, Witjes JA, Demkow T, Ferrero JM, et al. Multinational, double-blind, phase III study of prednisone and either satraplatin or placebo in patients with castrate-refractory prostate cancer progressing after prior chemotherapy: the SPARC trial. *J Clin Oncol* 2009;27:5431–8. [PubMed: 19805692]
44. Weidner N, Carroll PR, Flax J, Blumenfeld W, Folkman J. Tumor angiogenesis correlates with metastasis in invasive prostate carcinoma. *Am J Pathol* 1993;143:401–9. [PubMed: 7688183]
45. George DJ, Halabi S, Shepard TF, Vogelzang N J, Hayes DF, Small EJ, et al. Cancer and Leukemia Group B 9480. 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. [PubMed: 11448906]
46. Reese DMFP, Corry M, et al. A phase II trial of humanized anti-vascular endothelial growth factor antibody for the treatment of androgen-independent prostate cancer. *Prostate* 2001;3:65–70.
47. Dror Michaelson M, Regan MM, Oh WK, Kaufman DS, Olivier K, Michaelson SZ, et al. Phase II study of sunitinib in men with advanced prostate cancer. *Ann Oncol* 2009;20:913–20. [PubMed: 19403935]
48. Ning YM, Figg WD, Dahut WL. Reversal of docetaxel resistance with bevacizumab and thalidomide. *Clin Genitourin Cancer* 2009;7: E37–8. [PubMed: 19692321]
49. 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. *ASCO Meeting Abstracts* 2008;26:3599.
50. **NCT00519285**: A multicenter, randomized, double blind study comparing the efficacy and safety of aflibercept versus placebo administered every 3 weeks in patients treated with docetaxel/ prednisone for metastatic androgen-independent prostate cancer [cited 2011 Jan 17]. Available from: <http://www.clinicaltrials.gov>.
51. **ClinicalTrials.gov** NIH: Bethesda (MD); c2005 [updated 2010 6 18; cited 2010 Dec 2]. Phase III study of docetaxel and atrasentan versus docetaxel and placebo for patients with advanced hormone refractory prostate cancer. **NCT00134056**. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT00134056?term=NCT00134056&rank=1>.
52. Kelly WK, Halabi S, Carducci MA, George DJ, Mahoney JF, Stadler WM, et al. 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* 2010;28:LBA4511.
53. Araujo J, Armstrong AJ, Braud EL, Posadas E, Lon berg M, Gallick GE, et al. Dasatinib and docetaxel combination treatment for patients with castration-resistant progressive prostate cancer: A phase I/II study (CA180086). *ASCO Meeting Abstracts* 2009;27:5061.
54. Petrylak DP, Resto-Garces K, Tibyan M, Mohile SG. A phase I open-label study using lenalidomide and docetaxel in castration- resistant prostate cancer. *ASCO Meeting Abstracts* 2009;27:5156.
55. **NCT00988208**: A phase 3 study to evaluate the efficacy and safety of docetaxel and prednisone with or without lenalidomide in subjects with castrate-resistant prostate cancer [cited 2011 Jan 17]. Available from: <http://www.clinicaltrials.gov>.
56. Chi KN, Hotte SJ, Yu EY, Tu D, Eigl BJ, Tan nock I, et al. Randomized phase II study of docetaxel and prednisone with or without OGX-011 in patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 2010;28:4247–54. [PubMed: 20733135]
57. Goeckeler WF, Edwards B, Volkert WA, Holmes RA, Simon J, Wilson D. Skeletal localization of samarium-153 chelates: potential therapeutic bone agents. *J Nucl Med* 1987;28:495–504. [PubMed: 3572535]
58. Porfiri E, Collins SI, Barton D, Billingham L, McLaren D, Nixon GG, et al. Initial feasibility and safety results from a phase I I/II clinical trial to evaluate docetaxel (D) therapy in combination with zoledronic acid (ZA) {±} strontium-89 (Sr89) in hormone-refractory prostate cancer patients: ISRCTN12808747. *ASCO Meeting Abstracts* 2010;28:4677.
59. James ND, Caty A, Payne H, Borre M, Zonnenberg BA, Beuzeboc P, et al. Final safety and efficacy analysis of the specific endothelin A receptor antagonist zibotentan (ZD4054) in patients

with metastatic castration-resistant prostate cancer and bone metastases who were pain-free or mildly symptomatic for pain: a double-blind, placebo-controlled, randomized Phase II trial. *BJU Int* 2010;106:966–73. [PubMed: 20840318]

60. [ClinicalTrials.gov](http://clinicaltrials.gov) NIH: Bethesda (MD); 2008 [updated 2010 12 7; cited 2010 Dec 2]. A phase III trial of ZD4054 (zibotentan) (endothelin a antagonist) and docetaxel in metastatic hormone resistant prostate cancer (ENTHUSE M1C). [NCT00617669](http://clinicaltrials.gov/ct2/show/NCT00617669?term=NCT00617669&rank=1). Available from: <http://clinicaltrials.gov/ct2/show/NCT00617669?term=NCT00617669&rank=1>
61. Massard C, Fizazi K. Targeting continued androgen receptor signaling in prostate cancer. *Clin Cancer Res* 2011;17:3876–83. [PubMed: 21680543]
62. Attard G, Reid AH, A'Hern R, Parker C, Oommen NB, Folkard E, et al. Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. *J Clin Oncol* 2009;27:3742–8. [PubMed: 19470933]
63. Ryan CJ, Smith MR, Fong L, Rosenberg JE, Kantoff P, Raynaud F, et al. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. *J Clin Oncol* 2010;28:1481–8. [PubMed: 20159824]
64. Madan RA, Arlen PM. Abiraterone. *Cougar Biotechnology. I Drugs* 2006;9:49–55. [PubMed: 16374734]
65. Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science* 2009;324:787–90. [PubMed: 19359544]
66. Scher HI, Beer TM, Higano CS, Anand A, Taplin ME, Efstathiou E, et al. Prostate Cancer Foundation/Department of Defense Prostate Cancer Clinical Trials Consortium. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1–2 study. *Lancet* 2010;375:1437–46. [PubMed: 20398925]
67. Figg WD, Woo S, Zhu W, Chen X, Ajiboye AS, Steinberg SM, et al. A phase I clinical study of high dose ketoconazole plus weekly docetaxel for metastatic castration resistant prostate cancer. *J Urol* 2010;183:2219–26. [PubMed: 20399458]
68. Serafini AN, Houston SJ, Resche I, Quick DP, Grund FM, Ell PJ, et al. Palliation of pain associated with metastatic bone cancer using samarium-153 lexitronam: a double-blind placebo-controlled clinical trial. *J Clin Oncol* 1998;16:1574–81. [PubMed: 9552068]
69. Sartor O, Reid RH, Hoskin PJ, Quick DP, Ell PJ, Coleman RE, et al. Quadramet 424Sm10/11 Study Group. Samarium-153-Lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. *Urology* 2004;63:940–5. [PubMed: 15134985]
70. Nilsson S, Franzen L, Parker C, Tyrrell C, Blom R, Tennvall J, et al. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. *Lancet Oncol* 2007;8:587–94. [PubMed: 17544845]
71. Resche I, Chatal JF, Pecking A, Ell P, Duchesne G, Rubens R, et al. A dose-controlled study of 153Sm-ethylenediaminetetramethylenephosphonate (EDTMP) in the treatment of patients with painful bone metastases. *Eur J Cancer* 1997;33:1583–91. [PubMed: 9389919]
72. [ClinicalTrials.gov](http://clinicaltrials.gov) NIH: Bethesda (MD); c2010 [updated 2010 12 10; cited 2011 Jan 17]. A phase I/IIa study of safety and efficacy of alfaradin with docetaxel in patients with bone metastasis from castration-resistant prostate cancer. [NCT01106352](http://clinicaltrials.gov/ct2/show/NCT01106352?term=NCT01106352&rank=1). Available from: <http://clinicaltrials.gov/ct2/show/NCT01106352?term=NCT01106352&rank=1>.
73. Danila DC, Fleisher M, Scher HI. Circulating tumor cells as biomarkers in prostate cancer. *Clin Cancer Res* 2011;17:3903–12. [PubMed: 21680546]
74. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Prostate Cancer Clinical Trials Working Group. 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. [PubMed: 18309951]
75. Gulley JL, Drake CG. Immunotherapy for prostate cancer: recent advances, lessons learned, and areas for further research. *Clin Cancer Res* 2011;17:3884–91. [PubMed: 21680544]
76. Sartor AO, Oudard S, Ozguroglu M, Hansen S, Machiels JH, Shen L, et al. 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) In: Proceedings of the 2010 Genitourinary Cancers Symposium; 2010 3 5–7; San Francisco, CA. Alexandria (VA): ASCO; 2010 Abstract nr 9.

77. [NCT00744497](#): A randomized double-blind phase III trial comparing docetaxel combined with dasatinib to docetaxel combined with placebo in castration-resistant prostate cancer [cited 2011 Jan 17]. Available from: <http://www.clinicaltrials.gov>.

Figure 1.

Cabazitaxel differs from docetaxel by 2 methoxy side groups (circled), which are substituted for 2 hydroxyl groups in the structure of docetaxel. Adapted from Pal et al. (22).

Figure 2. OS with cabazitaxelprednisone demonstrates a survival advantage of 15.1 months compared to 12.7 months for mitoxantrone-prednisone (HR = 0.70). Reproduced with permission from Sartor et al. (76).

Table 1.

Potential mechanism of resistance to therapy in prostate cancer

Type of treatment	Potential mechanism of resistance
Taxane	Increase efflux of drug via P-glycoprotein pump
	Increased dynamic activity of the microtubules
	Alterations in taxane-binding sites
Hormonal therapy	Alterations in microtubule subunits or associated proteins
	Increased number and/or molecular stability of ARs
	Enhanced efficacy of AR coactivators within the nucleus
	Increased testosterone production via the cytochrome P17 pathway

Table 2.
Overall survival benefit in subsets of patients included in the phase III evaluation of cabazitaxel

Category	Factor	Hazard Ratio (95% CI)
ITT population	All Patients	0.69 (0.57–0.84)
Last docetaxel to random	<6 months	0.78 (0.62–0.97)
Last docetaxel to random	6 months	0.66 (0.46–0.96)
Total docetaxel dose	<225 mg/m ²	0.96 (0.46–2.03)
Total docetaxel dose	225–450 mg/m ²	0.61 (0.43–0.88)
Total docetaxel dose	450–675 mg/m ²	0.80 (0.56–1.16)
Total docetaxel dose	675–900 mg/m ²	0.73 (0.46–1.13)
Total docetaxel dose	900 mg/m ²	0.49 (0.31–0.79)
Progression	During last docetaxel treatment	0.67 (0.47–0.96)
Progression	Within first 3 months since last docetaxel dose	0.69 (0.52–0.91)
Progression	Between 4th and 6th month since last docetaxel dose	0.82 (0.48–1.40)
Progression	More than 6 months since	0.73 (0.35–1.53)

Abbreviation: ITT, intention to treat.

Table 3.

Proposed strategies to improve efficacy of taxanes in prostate cancer

Strategy	Description
Intermittent administration	Intermittent dosing of chemotherapy may allow time for patients to recover from toxicity and tolerate more prolonged treatment, which could improve long-term outcomes Break periods could be used to employ other therapies such as biologic or hormone-based treatments to delay time to taxane resistance
Combination therapy with platinum-based therapy	Joint targeting of microtubules and DNA may improve outcomes Phase II data suggest some patients may have improved responses to taxanes after a platinum agent has been added
Combination with angiogenesis inhibition	Although phase III data of a taxane with angiogenesis inhibition did not improve survival, substantial data support the importance of neovascular growth in prostate cancer Promising phase II data with a taxane and 2 antiangiogenesis agents may suggest that a maximal antiangiogenic blockade can enhance taxane-based therapy
Combination with novel hormonal agents	Changes in the AR signaling cascade may contribute to taxane resistance Combination therapies of taxanes with novel hormonal agents may delay the development of taxane-resistant prostate cancer
Combination with a radiopharmaceutical	Targeting the microenvironment of metastatic bone lesions with bone-targeted radiopharmaceuticals may enhance the clinical efficacy of systemic taxane-based therapy

Table 4.

Novel agents paired with docetaxel in phase III clinical trials in castration-resistant prostate cancer

Agent	Mechanism	Summary of Current Data
Aflibercept	VEGF decoy receptor	Phase I study of docetaxel with aflibercept suggested no exacerbation of docetaxel-related toxicity (49) Phase III study comparing docetaxel-prednisone to placebo or aflibercept currently completed accrual (50)
Atrasentan	Endothelin antagonist (nonspecific)	Phase III study evaluating docetaxel-prednisone with either placebo or atrasentan recently completed accrual (SWOG 0421; ref. 51)
Bevacizumab	VEGF-directed monoclonal antibody	No difference in OS in a phase III assessment of docetaxel-prednisone ± bevacizumab (CALGB 90401; ref. 52)
Dasatinib	Src inhibitor	Phase I and II study of docetaxel-prednisone with dasatinib showed safety and modest antitumor activity (53) Phase III study of docetaxel-prednisone with placebo or dasatinib completed accrual (77)
Lenalidomide	Antiangiogenic-immunomodulator	Phase I trial of docetaxel-prednisone + lenalidomide showed considerable PSA declines and modest antitumor activity (54) Phase III study evaluating docetaxel-prednisone with placebo or lenalidomide accrual underway (55)
OGX-011	Clusterin inhibitor	Numerically superior OS with OGX-011 in a randomized phase II study comparing docetaxel-prednisone ± OGX-011 (56) Phase III study evaluating docetaxel-prednisone ± OGX-011 underway (57)
⁸⁹ Sr	Radioisotope	Phase II and III study underway comparing docetaxel-prednisone with the following: (1) ⁸⁹ Sr, (2) zoledronic acid, (3) both, or (4) neither Initial results have highlighted no safety issues (58)
Zibotentan	Endothelin A antagonist	Numerically superior OS associated with zibotentan in a randomized phase II assessment (administered at 2 dose levels; ref. 59) Phase III study evaluating docetaxel-prednisone with placebo or zibotentan completed accrual (60)