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Management of Docetaxel Failures in Metastatic Castrate-Resistant Prostate Cancer

Sumanta K. Pal, MD¹, Brian Lewis, MD², and Oliver Sartor, MD^{2,3,*}

¹Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA

²Department of Medicine, Tulane University School of Medicine, New Orleans, LA

³Department of Urology, Tulane University School of Medicine, New Orleans, LA

SYNOPSIS

The treatment of metastatic castration resistant prostate cancer (mCRPC) has evolved markedly since the approval of docetaxel-based therapy in 2004. Since that time, 3 distinct agents have gained approval for use in the mCRPC setting, namely sipuleucel-T, cabazitaxel and abiraterone. Even more recently, phase III trials have demonstrated a survival benefit in association with the agents MDV-3100 and radium-223, and FDA approval is anticipated for both of these agents. Although these changes undoubtedly represent progress for the patient with mCRPC, for the practicing physician there is the additional challenge of determining the optimal sequencing for each of these agents. This dilemma is particularly relevant to the post-docetaxel setting, where the indication for several of these agents overlap. Herein, we provide the physician with detailed background on the efficacy and safety of these agents so as to provide a framework for their use in the clinic.

Introduction

In 1941, Huggins *et al* noted the dramatic effects of surgical castration in the treatment of metastatic prostate cancer.¹⁻² This landmark development revolutionized the therapy of the disease, and over time, pharmacologic methods of castration were developed as an alternative to surgical methods.³ Huggins recognized early on that “despite regressions of great magnitude, it is obvious that there are many failures of endocrine therapy to control the disease.”⁴ Though this disease state has undergone a number of nomenclature changes

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*Corresponding Author: Oliver Sartor, MD, Medical Director, Tulane Cancer Center, Laborde Professor of Cancer Research, Depts. of Medicine and Urology, Tulane Medical School, 1430 Tulane Ave., SL-42, New Orleans, LA 70112, Phone: (504) 988-7869, Fax: (504) 988-5059, osartor@tulane.edu.

Co-authors:

Sumanta K. Pal, MD, City of Hope Comprehensive Cancer Center, 1500 East Duarte Road, Duarte, CA 91010, Phone: (626)

256-4673, Fax: (626) 301-8233, spal@coh.org

Brian Lewis, MD, Tulane Medical School, 1430 Tulane Ave, SL-42, New Orleans, LA 70112, Phone: (504) 988-7869, Fax: (504) 988-5059, blewis@tulane.edu

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(including androgen-independent prostate cancer and hormone refractory prostate cancer), today we refer to this disease state as castration-resistant prostate cancer (CRPC), which may or not be metastatic. The onset of the metastatic CRPC (mCRPC) occurs at a median of about 9 years for years after androgen deprivation therapy (ADT) for patients initially treated with non-metastatic disease or 1–3 years after ADT for patients initially treated for metastatic disease.^{5–6}

For decades, clinical trials failed to show a definitive advantage with novel therapies for mCRPC.^{7–8} Two pivotal trials examining docetaxel-based regimens were the first to demonstrate an OS benefit in patients with mCRPC. In TAX 327, patients were randomized to receive either mitoxantrone/prednisone or docetaxel/prednisone in one of two schedules.⁹ Ultimately, docetaxel at a dose of 75 mg/m² intravenously (IV) every 3 weeks (q3wks) with prednisone daily led to a survival advantage over standard mitoxantrone/prednisone therapy (18.9 months vs 16.5 months, P=0.009). In Southwest Oncology Group (SWOG) trial 9916, patients were randomized to receive either docetaxel/estramusine or mitoxantrone/prednisone.¹⁰ Again, a survival advantage was noted with docetaxel-based therapy (17.5 months vs 15.6 months, P=0.02). The cumulative data from these studies led to the approval of docetaxel/prednisone based therapy for mCRPC on May 19, 2004.¹¹

Over the ensuing years, a number of different approaches were taken to build on the success of docetaxel in patients with mCRPC. One such approach was to explore combinations of novel therapies with docetaxel. Unfortunately, to date, these studies have proven somewhat disappointing.^{12–19} A second approach to the patient with mCRPC has been to explore the efficacy of novel therapies either prior to or subsequent to docetaxel therapy. These efforts have thus far proven to be more fruitful than explorations of combination therapy.²⁰ To date, the bulk of progress has been made in the post-docetaxel space – here, agents such as cabazitaxel, abiraterone, MDV3100, and radium-223 have all demonstrated statistically significant benefits in OS.^{21–24} Thus far, cabazitaxel/prednisone and abiraterone/prednisone are FDA approved. Although some agents (i.e., abiraterone, radium-223) may ultimately straddle pre- and post-docetaxel spaces,²⁵ the current review will focus on the current post-docetaxel strategies. The clinical data related to each agent will be reviewed in detail so as to provide the physician with a framework with which to approach the docetaxel-refractory patient.

Cabazitaxel

Structurally, docetaxel and the novel taxane cabazitaxel are quite similar, with two hydroxyl side chains (docetaxel) substituted for two methoxy groups (cabazitaxel) (Figure 1).²⁶ Both exert their preclinical activity through inhibition of microtubule disassembly, akin to other taxanes.^{27–29} However, early in its development, the preclinical activity of cabazitaxel was noted to be distinct from docetaxel. In a variety of cell lines (including P388 [lymphoblastic leukemia], HL60 [promyelocytic leukemia], and Calc18 [breast adenocarcinoma] models), cabazitaxel was noted to inhibit growth at relatively low concentrations, with an IC₅₀^{27–29} in the range of 3–29 nM.³⁰ The antitumor activity of cabazitaxel was maintained in cell lines that were resistant to other standard taxanes, as well. In murine xenograft models of prostate cancer (including the hormone resistant DU145 cell line), near complete tumor regressions were observed.^{31–32}

The encouraging preclinical data for cabazitaxel led to initiation of a phase I clinical trial.³³ In this study, 25 patients with advanced solid tumors were treated with doses of cabazitaxel ranging from 10 to 25 mg/m². Eight patients with advanced prostate cancer were enrolled on the study, representing the largest subgroup based on tumor type. Pharmacokinetic data from this study indicated a triphasic model of elimination ($t_{1/2}$ = 2.5 minutes, 1.3 hours, and 77.3

hours for the 3 phases, respectively). Notably, the recommended phase II dose emerging from the study was 20 mg/m², given dose-limiting toxicities (DLTs) of febrile neutropenia and grade 4 neutropenia occurring at a dose of 25 mg/m². Two patients attained a partial response in this phase I effort, both in patients with advanced prostate cancer who had received prior mitoxantrone and docetaxel, respectively.

A separate phase I study examined doses of cabazitaxel ranging from 10 to 30 mg/m² IV q3wks; the recommended phase II dose in this effort was 25 mg/m².³⁴ Akin to the previously noted phase I study, the most frequent toxicities were neutropenia, febrile neutropenia, diarrhea and infection. This study helped establish the extent of *ex vivo* plasma protein binding (approximately 92%); cabazitaxel showed high binding to both lipoproteins and albumin. The intra-patient variability of the area under the curve between 0–48 hours (AUC_{0–48}) was also ascertained in this study, and was estimated to be approximately 27%.

A phase II exploration of cabazitaxel in heavily pre-treated breast cancer utilized a phase II dose of 20 mg/m² as a starting dose, but allowed escalation to 25 mg/m² provided tolerance of the initial dose level.³⁵ Although originally designed as a 3-arm, randomized phase II study evaluating both cabazitaxel and a distinct novel taxane (larotaxel),³⁶ the trial design was modified due to poor accrual to include just one arm. Patients may have received prior taxane in either the adjuvant or metastatic setting. With a total of 67 patients, the ORR was 14%, and the median duration of response was 7.6 months (range, 2.6–18.7 months). Although two complete responses (CRs) were observed, several concerning safety signals were seen in this study, with two deaths due to non-hematologic toxicity noted within 30 days of study treatment.

A rather unique element of the clinical development of cabazitaxel is its evolution from phase I to phase III assessment in prostate cancer – there was no phase II evaluation of the drug outside of the setting of breast cancer. The phase III TROPIC study built on the preclinical efficacy of cabazitaxel seen in preclinical models of hormone-resistant prostate cancer, and the responses seen in the phase I assessment.²⁴ In this study, 775 patients with docetaxel refractory disease were randomized to receive either cabazitaxel at 25 mg/m² IV q3wks with prednisone or mitoxantrone with prednisone. The definition of docetaxel-refractory disease employed in TROPIC included either (1) response evaluation criteria in solid tumors (RECIST)-based progression, or (2) two consecutive PSA rises at least one week apart. Patients were initially permitted to enroll with any prior docetaxel exposure, but the study was later modified to include patients who had at least a cumulative docetaxel dose of 225 mg/m².^{37–38}

The study met its primary endpoint, demonstrating a significant improvement in median OS from 12.7 months with mitoxantrone/prednisone to 15.1 months with cabazitaxel/prednisone (P<0.001).²⁴ Furthermore, PFS was improved with cabazitaxel-based therapy (2.8 months vs 1.4 months, P<0.0001). Pain relief, as assessed by the McGill-Melzack pain questionnaire, was not distinct between arms. The positive survival advantage led to the FDA approval of cabazitaxel on June 17, 2010.³⁹ Interestingly, post-hoc analyses show that this survival advantage actually extends to the overall survival time from first docetaxel usage.⁴⁰ Specifically, median OS was 29 months from the time of first docetaxel use in patients receiving subsequent cabazitaxel therapy, as compared to 25 months in patients receiving subsequent mitoxantrone therapy. Furthermore, a survival benefit was seen in subgroups that discontinued use of docetaxel therapy for progression, and in subgroups that discontinued use of docetaxel therapy for other reasons (adverse events, intolerance, etc.).⁴¹ The findings in patients with progression while on docetaxel underscore the distinction between docetaxel and cabazitaxel.

As in earlier experiences with cabazitaxel, the most common adverse event noted in the phase III study was neutropenia, with grade 3 neutropenia occurring in 82% of patients, and 8% of patients developing febrile neutropenia.²⁴ One factor that may account for the high frequency of neutropenia and related events seen in TROPIC was the prohibition of prophylactic growth factor use. With the first cycle of therapy with cabazitaxel, patients were not allowed to use these agents, although they could be implemented subsequently. Recommendations accompanying the FDA approval of cabazitaxel recommend use of growth factor support in at-risk groups, including (1) older patients (age > 65), (2) recipients of extensive prior radiation, (3) patients with poor nutritional status, (4) patients with prior documented episodes of febrile neutropenia, (5) patients with poor performance status, and (6) patients with other serious medical co-morbidities.⁴² It is foreseeable that these criteria encompass the majority of patients in a typical prostate cancer clinic. A retrospective subset analysis of patients that received prophylactic growth factor support from cycle 2 of cabazitaxel therapy onwards did suggest a dramatic decline in grade > 3 neutropenia (23.7% vs 57.7%; $P < 0.0001$).⁴³ These data support the more aggressive use of growth factors in many patients receiving cabazitaxel therapy today in the clinic.

Other notable toxicities associated with cabazitaxel include diarrhea – several deaths secondary to treatment-related diarrhea were seen in the TROPIC study. Recommendations accompanying the publication of the TROPIC data suggest vigilant monitoring for dehydration, with prompt administration of anti-diarrheals and fluids if this toxicity is incurred. Other frequent non-hematologic toxicities include fatigue and asthenias. With the caveats of cross-trial comparisons, several toxicities (i.e., neuropathy and alopecia) appear less prevalent with cabazitaxel therapy.

Abiraterone

Ketoconazole has been used for patients with CRPC since the 1980s when it was noted to decrease testosterone in patients being treated for anti-fungal indications.⁷ The mechanism of the testosterone decline is enzymatic inhibition of several enzymatic steps in the androgen synthetic pathway, most notably 17- α -hydroxylase/17,20-desmolase (CYP17). Because inhibition of the 17- α -hydroxylase is associated with decreased cortisol synthesis, ketoconazole at doses of 600–1200 mg per day is typically given with glucocorticoids such as prednisone, hydrocortisone, or dexamethasone.

Newer CYP17 inhibitors such as abiraterone also require glucocorticoids, not only to replace cortisol but also to feedback on the pituitary to diminish the ACTH stimulation which stimulates increased production of mineralocorticoids.⁴⁴ Abiraterone was initially developed by scientists at the Institute for Cancer Research in London. De Bono and colleagues were the first to test the abiraterone/prednisone in prostate cancer clinical trials and excellent initial results were reported for both tolerability and PSA declines.⁴⁴ Abiraterone results in a relatively complete inhibition of androgen and estrogen synthesis and substantially decrease, even in castrate men, serum levels of testosterone, estradiol, dehydroepiandrosterone, and androstenedione.

Oral abiraterone with 5 mg bid prednisone is now FDA approved on the basis of a phase III trial with 1195 patients in the mCRPC post-docetaxel ketoconazole-naïve setting.²¹ This trial was stopped at an interim analysis after meeting the primary endpoint of overall survival. This trial randomized patients to receive prednisone 5 mg bid plus 1000 mg of abiraterone acetate as compared to patients receiving prednisone/placebo. At 12.8 months median patient follow-up, overall survival in the abiraterone/prednisone arm was 14.8 months as compared to 10.9 months in the prednisone alone arm (hazard ratio, 0.65; $P < 0.001$). Secondary end points, including time to PSA progression (10.2 vs. 6.6 months;

$P < 0.001$) and PSA response rate (29% vs. 6%, $P < 0.001$), also favored the abiraterone-treated patients. The agent was well tolerated though mineralocorticoid side effects (fluid retention, hypokalemia, and hypertension) were clearly more common in the abiraterone treated patients.²¹ Another phase III abiraterone interim result from asymptomatic or minimally symptomatic ketoconazole-naïve patients conducted in the pre-docetaxel setting has recently been reported by the sponsor in a press release.²⁵

MDV3100

Of the 3 FDA approved antiandrogens (bicalutamide, nilutamide and flutamide), bicalutamide has the highest affinity for the androgen receptor by a factor of 2 to 4.⁴⁵ MDV3100 is a novel androgen receptor inhibitor that has 5 to 8 times the affinity for the androgen receptor as compared to bicalutamide; furthermore, unlike bicalutamide and flutamide, the agent has no agonist activity. MDV3100 also inhibits the androgen receptor nuclear translocation, DNA binding and cofactor activation.⁴⁶

MDV3100 was evaluated in a phase I/II clinical trial whereby 140 patients with castrate resistant prostate cancer were given escalated doses of the drug from 30 to 600 mg oral daily.⁴⁷ Of the patients studied, 54% had previous treatment with chemotherapy and 78% had bone metastatic disease. Time to radiographic progression (TTRP) was 47 weeks in the intent to treat population, and was 29 weeks in the subset of patients with prior chemotherapy exposure. The time to PSA progression by PCWG2 criteria was 32 weeks for the entire population, 21 weeks for the patients with a history of prior chemotherapy and 41 weeks for the chemotherapy-naïve population. The percent of patients with a maximum PSA decline $\geq 50\%$ was 56% for the entire cohort. The most common grade 2 adverse events were fatigue, nausea, dyspnea and anorexia. Two of the 140 patients had a seizure and the most common cause of dose reduction or discontinuation was fatigue.

These encouraging data lead to phase III placebo controlled trial where 1,199 patients who had received ≥ 2 docetaxel-based regimens were randomized 2:1 to receive MDV3100 at 160 mg oral daily or placebo.²³ The primary endpoint of the study was OS. Secondary endpoints included TTRP, time to PSA progression and PSA response. There was found to be an OS benefit of 4.8 months, with median overall survival of 13.6 months in placebo-treated patients and 18.4 months MDV3100-treated patients ($P < 0.001$). TTRP was 8.3 months for MDV3100 vs 2.9 months for placebo, and the time to PSA progression was 8.3 months for MDV3100 vs 3 months for placebo ($P < 0.0001$ for both). There was also a significant improvement in PSA response, with 54% and 1.5% of patients having PSA reductions $\geq 50\%$ from baseline in the MDV3100 and placebo arms, respectively. The most common adverse event was fatigue, with 33% of patients in the MDV3100 group and 29% of patients in the placebo group reporting fatigue of any grade. This trial should lead to the FDA approval of MDV3100 in the near future. The phase III PREVAIL trial comparing MDV3100 to placebo in chemotherapy naïve men is currently enrolling patients.

Bone-Targeted Therapy

When metastatic, prostate cancer involves bone in approximately 70% of cases.⁴⁸ Thus, the concept of bone targeted therapy has long been considered an attractive and logical concept. These agents are appropriate in either the pre- or post-docetaxel space. FDA approved bone targeted products for bone metastatic CRPC include zoledronic acid, denosumab, strontium-89 and samarium-153 lexidronam.^{49–50} Zoledronate and denosumab were approved by regulatory agencies as a consequence of trials demonstrating decreased rates of skeletal related events (pathologic fractures, radiation to bone, surgery to bone, or spinal cord compression).^{49–50} The radionuclides were approved as a consequence of meeting

various palliative endpoints.^{51–53} To date, however, none of these agents have improved overall survival in a phase III trial.

Radium-223

In contrast, radium-223 is a novel bone-targeted alpha-emitter recently shown to improve overall survival in a very recently reported large phase III study.²² Strontium-89 is a calcium homologue that binds to the stroma as a consequence of calcium being deposited in the newly formed bone of osteoblastic metastases. Radium-223 also functions as a calcium homologue and binds avidly to regions of osteoblastic lesions (Figure 2 and 3 – AU: placement of Figure 3 OK?). Instead of releasing a beta particle as an emission, radium-223 emits an alpha-particle. Alpha particles are comprised of two protons and two neutrons and are approximately 7300 times larger than an electron. Alpha particles are efficient in causing DNA double strand breaks which are highly lethal given their propensity to cause non-reparable DNA double-strand breaks.⁵⁴ Despite their destructive nature, the distance traveled in tissues is discrete. Whereas beta particles travel millimeters in tissue, alpha particles typical travel only microns. Thus the combination of high lethality and short range of action are typical of targeted alpha-emitters such as radium-223.

In initial clinical trials, radium-223 was associated with minimal toxicities and a suggestion of tumor responses.^{55–56} A randomized phase II trial with four doses of radium-223 suggested a survival advantage with minimal toxicity,⁵⁶ this leading to a randomized phase III trial (ALSYMPCA) which enrolled over 900 patients.²² Patients were required to be either post-docetaxel or be unsuitable for docetaxel. Unsuitability was determined by the treating physician rather than by objective criteria. In addition, the eligibility criteria for the phase III was bone-metastatic symptomatic CRPC with no visceral metastases and no lymph nodes over 3 cm in size. Patients refusing docetaxel were also allowed to participate. Standard hematological and biochemical parameters were required for trial entry. Performance status 0–2 was required. Patients were randomized 2:1 to radium-223 or placebo. Best supportive care was allowed in both arms. This could consist of various secondary hormonal manipulations. Glucocorticoids, estrogens, anti-estrogens were typically used. Concomitant chemotherapy or hemi-body radiations were not allowed. Patients were stratified by prior docetaxel use, alkaline phosphatase greater or less than 220 U/L, and bisphosphonate use (yes/no). The primary endpoint was overall survival; secondary endpoints included both skeletal related events (SREs) and a variety of biochemical parameters including PSA. The SREs were clinically relevant events. Unlike zoledronate and denosumab, asymptomatic bone survey detected fractures were not tabulated. Interesting, no imaging was required and time to radiographic time to progression was not captured.

The ALSYMPCA trial was stopped at the first planned interim analysis (after 314 deaths 809 enrolled patients) as a consequence of meeting exceeding a pre-specified overall survival threshold for early termination.²² The early termination threshold for overall survival was $P=0.00306$ and the observed P value was 0.00185. The median survival was 11.2 months in the placebo arm versus 14.0 months in the isotopic arm ($HR=0.695$, 95% CI 0.552–0.875). The secondary endpoints including SREs and PSA progression free survival were also positive.⁵⁷ The SRE rate was reduced by 31% ($HR=0.61$, 95% CI, 0.461–0.807, $P=0.00046$). Three of the four pre-specified components of skeletal related event rates were improved in the radium treatment arm; radiation to bone (HR 0.65, $P=0.0038$) spinal cord compression (HR 0.44, $P=0.016$), and pathologic fracture (HR 0.45, $P=0.013$). This is the first trial in our knowledge to decrease rates of spinal cord compression in prostate cancer.

Toxicity was low in the radium-223 arm.²² The overall adverse event rate and the serious adverse event rate were lower in the isotopic arm than placebo. Grade 3/4 thrombocytopenia was 4% in the radionuclide arm and 2% in placebo. Grade 3/4 neutropenia was 2% in the radium arm and 1% in the placebo arm. The radium-223 submission to various national regulatory agencies is ongoing at this time but given the overall survival endpoint results and the toxicity profile, it is anticipated that radium-223 will be part of the armamentarium in the near future.

CONCLUSIONS

There is considerable current debate on the optimal sequence of mCRPC therapies. This debate is not based on clinical trials but rather inferences and various biases. No sequence of treatments can be recommended on the basis of clinical trial data but, as mentioned above, both cabazitaxel and abiraterone are only approved in the post-docetaxel mCRPC patient.

Perhaps the current state of affairs in mCRPC is best understood from an historic perspective (Table 1). Prior to 2004 and the randomized docetaxel trials (TAX327 and SWOG 9916), no treatment had been demonstrated to improve OS in a large phase III trial. Subsequent to 2004, the concept of the pre-and post-docetaxel space has defined the regulatory and clinical approach to mCRPC. Such a definition is rational but not biologically based. In 2010, sipuleucel-T was approved for men with asymptomatic or minimally symptomatic metastatic CRPC. A small percentage (roughly 18%) of patients in the phase III sipuleucel-T were docetaxel pre-treated. The two most recent FDA approved agents, cabazitaxel and abiraterone, are specifically approved in patients with prior docetaxel exposure and both prolong survival. Toxicities vary considerably between abiraterone and cabazitaxel and this can form the basis for treatment selection in some patients. The finding that abiraterone/prednisone prolong survival in the post-docetaxel mCRPC disease state clearly indicates that these patients remain sensitive to hormonal manipulations. Agents that do not prolong survival may also be appropriate in the post-docetaxel CRPC patient. Strontium-89 and samarium-153 lexidronam are bone targeted agents appropriate for bone-pain palliation. The zoledronic acid and denosumab indications are clear and can reduce the risk of skeletal related events.

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References

1. Huggins C, Hodges CV. Studies on Prostatic Cancer. I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate. *Cancer Res.* 1941; 1:293–7.
2. Huggins C, Stevens RE Jr, Hodges CV. Studies on Prostate Cancer: II. The effects of castration on advanced carcinoma of the prostate gland. *Arch Surg.* 1941; 43:209–23.
3. Labrie F, Dupont A, Bélanger A, et al. Treatment of prostate cancer with gonadotropin-releasing hormone agonists. *Endocr Rev.* 1986 Feb; 7(1):67–74. [PubMed: 3514203]
4. [last accessed March 21, 2012] Nobel Prize Lecture by Charles Huggins. Transcript available at http://www.nobelprize.org/nobel_prizes/medicine/laureates/1966/huggins-lecture.pdf
5. Klotz L, O'Callaghan CJ, Ding K, et al. A phase III randomized trial comparing intermittent versus continuous androgen suppression for patients with PSA progression after radical therapy: NCIC CTG PR.7/SWOG JPR.7/CTSU JPR. 7/UK Intercontinental Trial CRUKE/01/013 ASCO Meeting Abstracts. 2011; 29:3.
6. Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data

- from Southwest Oncology Group Trial 9346 (INT-0162). *J Clin Oncol*. 2006; 24:3984–90. [PubMed: 16921051]
7. Small EJ, Halabi S, Dawson NA, et al. Antiandrogen Withdrawal Alone or in Combination With Ketoconazole in Androgen-Independent Prostate Cancer Patients: A Phase III Trial (CALGB 9583). *J Clin Oncol*. 2004; 22:1025–33. [PubMed: 15020604]
 8. 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. [PubMed: 8656243]
 9. 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. [PubMed: 15470213]
 10. Petrylak DP, Tangen CM, Hussain MHA, et al. Docetaxel and Estramustine Compared with Mitoxantrone and Prednisone for Advanced Refractory Prostate Cancer. *N Engl J Med*. 2004; 351:1513–20. [PubMed: 15470214]
 11. [accessed July 14, 2012] <http://www.cancer.gov/cancertopics/druginfo/fda-docetaxel>
 12. Kelly WK, Halabi S, Carducci MA, 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 (Meeting Abstracts)*. 2010; 28:LBA4511.
 13. Ortholan C, Durivault J, Hannoun-Levi JM, et al. Bevacizumab/docetaxel association is more efficient than docetaxel alone in reducing breast and prostate cancer cell growth: a new paradigm for understanding the therapeutic effect of combined treatment. *Eur J Cancer*. 2010; 46:3022–36. [PubMed: 20729074]
 14. [accessed July 14, 2012] <http://www.astrazeneca.com/Media/Press-releases/Article/0022011AstraZeneca-halts-phase-III-trial-of-ZIBOTENTAN>
 15. [accessed July 14, 2012] <http://investor.regeneron.com/releasedetail.cfm?releaseid=661995>
 16. Scher HI, Jia X, Chi K, et al. Randomized, Open-Label Phase III Trial of Docetaxel Plus High-Dose Calcitriol Versus Docetaxel Plus Prednisone for Patients With Castration-Resistant Prostate Cancer. *Journal of Clinical Oncology*. 2011; 29:2191–8. [PubMed: 21483004]
 17. Nelson JB, Fizazi K, Miller K, et al. Phase III study of the efficacy and safety of zibotentan (ZD4054) in patients with bone metastatic castration-resistant prostate cancer (CRPC). *ASCO Meeting Abstracts*. 2011; 29:117.
 18. Quin DI, Tangen CM, Hussain M, et al. SWOG S0421: Phase III study of docetaxel (D) and atrasentan (A) versus docetaxel and placebo (P) for men with advanced castrate resistant prostate cancer (CRPC). *J Clin Oncol*. 2012; 30 (suppl; abstr 4511).
 19. Small, E.; Demkow, T.; Gerritsen, WR., et al. A phase III trial of GVAX immunotherapy for prostate cancer in combination with docetaxel versus docetaxel plus prednisone in symptomatic, castration-resistant prostate cancer (CRPC). Presented at the 2009 Genitourinary Cancers Symposium; San Francisco, CA. 2009. p. Abstract 7
 20. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010; 363:411–22. [PubMed: 20818862]
 21. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011; 364:1995–2005. [PubMed: 21612468]
 22. Parker C, Heinrich D, O'Sullivan JM, et al. Overall survival benefit and safety profile of radium-223 chloride, a first-in-class alpha-pharmaceutical: Results from a phase III randomized trial (ALSYMPCA) in patients with castration-resistant prostate cancer (CRPC) with bone metastases. *ASCO Meeting Abstracts*. 2012; 30:8.
 23. Scher HI, Fizazi K, Saad F, et al. Effect of MDV3100, an androgen receptor signaling inhibitor (ARSI), on overall survival in patients with prostate cancer postdocetaxel: Results from the phase III AFFIRM study. *ASCO Meeting Abstracts*. 2012; 30:LBA1.
 24. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *The Lancet*. 2010; 376:1147–54.

25. Kawasaki Y, Ito A, Withers DA, et al. Ganglioside DSGb5, preferred ligand for Siglec-7, inhibits NK cell cytotoxicity against renal cell carcinoma cells. *Glycobiology*. 2010; 20:1373–9. [PubMed: 20663960]
26. Madan RA, Pal SK, Sartor O, Dahut WL. Overcoming chemotherapy resistance in prostate cancer. *Clin Cancer Res*. 2011; 17:3892–902. [PubMed: 21680545]
27. Caplow M, Zeeberg B. Dynamic Properties of Microtubules at Steady State in the Presence of Taxol. *European Journal of Biochemistry*. 1982; 127:319–24. [PubMed: 6128228]
28. Kumar N. Taxol-induced polymerization of purified tubulin. Mechanism of action *Journal of Biological Chemistry*. 1981; 256:10435–41.
29. White J, Rao G. Effects of a microtubule stabilizing agent on the response of platelets to vincristine. *Blood*. 1982; 60:474–83. [PubMed: 6124288]
30. Bissery M-C, Bouchard H, Riou J, Vrignaud P, Combeau C, Bourzat JD. Preclinical evaluation of TXD258, a new taxoid. *Proceedings of the American Association for Cancer Research*. 2000; 41:Abstr 1364.
31. Vrignaud P, Lejeune P, Chaplin D, Lavelle F, Bissery M-C. In vivo efficacy of TXD258, a new taxoid, against human tumor xenografts. *Proceedings of the American Association for Cancer Research*. 2000; 41:Abstr 1365.
32. Stone KR, Mickey DD, Wunderli H, Mickey GH, Paulson DF. Isolation of a human prostate carcinoma cell line (DU 145). *Int J Cancer*. 1978; 21:274–81. [PubMed: 631930]
33. Mita AC, Denis LJ, Rowinsky EK, 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. *Clinical Cancer Research*. 2009; 15:723–30. [PubMed: 19147780]
34. [last accessed March 22, 2012] FDA Clinical Pharmacology and Biopharmaceutical Reviews (Application 201023). Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/201023s000ClinPharmR.pdf
35. Dieras V, Limentani S, Romieu G, et al. Phase II multicenter study of larotaxel (XRP9881), a novel taxoid, in patients with metastatic breast cancer who previously received taxane-based therapy. *Ann Oncol*. 2008; 19:1255–60. [PubMed: 18381372]
36. Metzger-Filho O, Moulin C, de Azambuja E, Ahmad A. Larotaxel: broadening the road with new taxanes. *Expert Opin Investig Drugs*. 2009; 18:1183–9.
37. 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. [PubMed: 18309951]
38. Di Lorenzo G, Buonerba C, Autorino R, De Placido S, Sternberg CN. Castration-resistant prostate cancer: current and emerging treatment strategies. *Drugs*. 70:983–1000. [PubMed: 20481655]
39. [accessed July 14, 2012] <http://www.cancer.gov/cancertopics/druginfo/fda-cabazitaxel>
40. Sartor AO, Oudard S, Ozguroglu M, et al. Survival benefit from first docetaxel treatment for cabazitaxel plus prednisone compared with mitoxantrone plus prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) enrolled in the TROPIC trial. *ASCO Meeting Abstracts*. 2011; 29:4525.
41. De Bono JS, Oudard S, Ozguroglu M, et al. A subgroup analysis of the TROPIC trial exploring reason for discontinuation of prior docetaxel and survival outcome of cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC). *ASCO Meeting Abstracts*. 2011; 29:4526.
42. [accessed July 14, 2012] http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/2010231b1.pdf
43. Ozguroglu M, Oudard S, Sartor AO, et al. Effect of G-CSF prophylaxis on the occurrence of neutropenia in men receiving cabazitaxel plus prednisone for the treatment of metastatic castration-resistant prostate cancer (mCRPC) in the TROPIC study. *ASCO Meeting Abstracts*. 2011; 29:144.
44. Attard G, Reid AHM, A'Hern R, et al. Selective Inhibition of CYP17 With Abiraterone Acetate Is Highly Active in the Treatment of Castration-Resistant Prostate Cancer. *J Clin Oncol*. 2009 JCO. 2008.20.0642.
45. Kolvenbag GJ, Furr BJ, Blackledge GR. Receptor affinity and potency of non-steroidal antiandrogens: translation of preclinical findings into clinical activity. *Prostate Cancer Prostatic Dis*. 1998; 1:307–14. [PubMed: 12496872]

46. Tran C, Ouk S, Clegg NJ, et al. Development of a Second-Generation Antiandrogen for Treatment of Advanced Prostate Cancer. *Science*. 2009; 324:787–90. [PubMed: 19359544]
47. Scher HI, Beer TM, Higano CS, et al. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1–2 study. *Lancet*. 2010; 375:1437–46. [PubMed: 20398925]
48. Wang C, Shen Y. Study on the distribution features of bone metastases in prostate cancer. *Nucl Med Commun*. 2012; 33:379–83. [PubMed: 22293499]
49. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*. 2011; 377:813–22. [PubMed: 21353695]
50. Saad F, Gleason DM, Murray R, et al. Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients With Metastatic Hormone-Refractory Prostate Cancer. *Journal of the National Cancer Institute*. 2004; 96:879–82. [PubMed: 15173273]
51. Lewington VJ, McEwan AJ, Ackery DM, et al. A prospective, randomised double-blind crossover study to examine the efficacy of strontium-89 in pain palliation in patients with advanced prostate cancer metastatic to bone. *Eur J Cancer*. 1991; 27:954–8. [PubMed: 1716935]
52. Porter AT, McEwan AJ, Powe JE, et al. Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. *Int J Radiat Oncol Biol Phys*. 1993; 25:805–13. [PubMed: 8478230]
53. Sartor O. Overview of samarium sm 153 lexidronam in the treatment of painful metastatic bone disease. *Rev Urol*. 2004; 6 (Suppl 10):S3–S12. [PubMed: 16985930]
54. Ritter MA, Cleaver JE, Tobias CA. High-LET radiations induce a large proportion of non-rejoining DNA breaks. *Nature*. 1977; 266:653–5. [PubMed: 859634]
55. Nilsson S, Franzen L, Parker C, 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]
56. Nilsson S, Strang P, Aksnes AK, et al. A randomized, dose-response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer. *Eur J Cancer*. 2012
57. Sartor AO, Heinrich D, Helle SI, et al. Radium-223 chloride impact on skeletal-related events in patients with castration-resistant prostate cancer (CRPC) with bone metastases: A phase III randomized trial (ALSYMPCA). *ASCO Meeting Abstracts*. 2012; 30:9.

Figure 1. Structure of cabazitaxel

Highlighted are two entities in the cabazitaxel chemical structure that differ from docetaxel – namely, the two methoxy groups of cabazitaxel are substituted with hydroxyl side chains in docetaxel.

Figure 2. Mechanism of abiraterone

Abiraterone inhibits critical steps in the biosynthetic pathway of glucocorticoids and testosterone/estradiol.

Figure 3. Normal bone (a) as compared to osteoblastic lesions (b) in a canine model
Note that agents such as radium-223 demonstrate preferential uptake in osteoblastic lesions.

Table 1

FDA approved agents for the treatment of mCRPC.

Agent	Date	Disease State	Primary Endpoint
Estramustine	1981	mCRPC	Disease responses
Strontium-89	1993	mCRPC	Pain reduction
Mitoxantrone/prednisone	1996	mCRPC	Pain reduction
Samarium-153	1997	mCRPC	Pain reduction
Zoledronic acid	2002	mCRPC (to bone)	SRE reduction
Docetaxel/prednisone	2004	mCRPC	Prolonged survival
Sipuleucel-T	2010	mCRPC (asymptomatic)	Prolonged survival
Cabazitaxel/prednisone	2010	mCRPC (post-docetaxel)	Prolonged survival
Denosumab	2010	mCRPC (to bone)	SRE reduction
Abiraterone/prednisone	2011	mCRPC (post-docetaxel)	Prolonged survival