Practical guide to the use of chemotherapy in castration resistant prostate cancer

Daniel P. Petrylak, MD
Department of Medicine (Medical Oncology) and Urology, Yale Cancer Center, New Haven, Connecticut, USA

PETRYLAK DP. Practical guide to the use of chemotherapy in castration resistant prostate cancer. *Can J Urol* 2014;21(Suppl 1):77-83.

Introduction: *Chemotherapy, once thought to be toxic and ineffective in men with castration resistant prostate cancer (CRPC), has a significant impact on survival and quality-of-life in these patients. This article summarizes recent studies performed with two Food and Drug Administration (FDA) approved agents which have improved survival in men with CRPC, docetaxel and cabazitaxel.*

Materials and methods: *The literature on cytotoxic chemotherapy for castration resistant prostate cancer was reviewed. The individual efficacy, mechanisms of chemotherapeutic action, and appropriate disease states of administration were identified. Recent clinical trial results of chemotherapy combined with targeted agents was also reviewed.*

Results: *Front line cytotoxic therapy consists of docetaxel combined with prednisone. In two randomized trials, docetaxel based therapy demonstrated a 20%-24% improvement in survival over the palliative standard of care, mitoxantrone combined with prednisone. Eight randomized trials combining docetaxel/prednisone with other antiangiogenic, bone targeted, vaccine or metabolic therapies failed to demonstrate an improvement in survival over docetaxel alone. Cabazitaxel, an analogue of docetaxel which has activity in taxane resistant cell lines, is approved by the FDA, for use in CRPC patients who have previous exposure to docetaxel.*

Conclusions: *Docetaxel combined with prednisone remains the standard of care as first line cytotoxic therapy for CRPC. Cabazitaxel is an effective second line cytotoxic agent that improves survival; studies are underway comparing cabazitaxel to docetaxel as first line chemotherapy. Given its lack of survival benefit, as well as the emergence of new treatments for prostate cancer, mitoxantrone has a diminished role in the treatment of CRPC.*

Key Words: castration resistant prostate cancer, docetaxel, cabazitaxel, chemotherapy

Introduction

It is estimated that more than 29000 men will die from metastatic prostate cancer in 2014, making it the second leading cause of male cancer death.[1] The initial treatment for metastatic disease is surgical or medical castration; reduction in testosterone to levels of less than 50 ng/dL can rapidly and dramatically result in prostate tumor regression.[2] Clinical response to androgen blockade is manifested by a relief in pain from boney metastases, improvement in neurologic symptoms from spinal cord compression, and a decline in serum prostate-specific antigen (PSA). Despite initial clinical and symptomatic improvement, nearly all men will progress to castration resistant prostate cancer (CRPC). This state of disease is defined as progression of face of castrate testosterone levels, historically have a dismal prognosis with median survival times of 9-12 months. In addition, the morbidity associated with CRPC is significant as metastases to bone can lead to spinal cord compression, fractures, pain, cachexia, anemia, and ultimately death.

In the 1990s, the management of CRPC was limited to palliation of symptoms, due to a lack of effective

Address correspondence to Dr. Daniel P. Petrylak, Department of Urology and Medical Oncology, Yale University Cancer Center, 789 Howard Ave, FMP 312, New Haven, CT 06519 USA

treatments. Historically, chemotherapy for advanced prostate cancer was viewed as toxic and ineffective. Two reviews of single agent cytotoxic therapy in men with CRPC demonstrated that objective responses to chemotherapy were 6.5% to 8.7%, with no improvement in survival.[3,4] The combination of mitoxantrone-prednisone was approved by the Food and Drug Administration (FDA) based on palliation of bone pain; three randomized trials also demonstrated modest improvements in time to progression when mitoxantrone combined with corticosteroids was compared to corticosteroids alone.[5-7] Until 2004, CRPC was considered a chemotherapy resistant disease with no randomized study demonstrating a survival of chemotherapy.

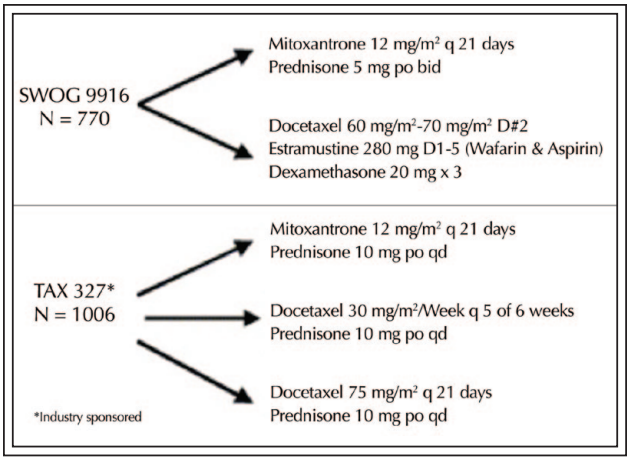

Figure 1. Study designs of SWOG 99-16 and TAX 327.

Docetaxel for CRPC

A semisynthetic taxane derived from the needles of *Taxus baccata*, docetaxel. Docetaxel reversibly stabilizes microtubules and prevents depolymerization.[8] Apoptosis results from accumulation of microtubules, as well as through phosphorylation of an oncoprotein, Bcl-2.[9] Both in vitro and in vivo studies found docetaxel to be effective against a wide range of human cancer cell lines, including the prostate cancer cell lines DU 145, PC-3 and LNCaP.[10,11] Phase I and II trials of docetaxel administered as a single agent or in combination with estramustine phosphate demonstrated PSA decline rates of > 50% in 36%-69% of treated patients, objective response rates of 17%-38% and median survivals of 20-23 months.[12-15] Two phase III trials compared docetaxel-based combination regimens with standard mitoxantrone/prednisone in men with progressive CRPC, Figure 1 and Table 1.

TAX327 was an international multi-center study that compared two different dosing schedules of docetaxel/prednisone with mitoxantrone/prednisone for metastatic CRPC.[16] No history of any prior chemotherapy in these CRPC patients was permitted except for estramustine. One thousand six patients were randomized to one of three arms: 1) docetaxel 75 mg/m^2 every 3 weeks; docetaxel 30 mg/m^2 weekly for 5 of 6 weeks or mitoxantrone 12 mg/m^2 every 3 weeks. Prednisone at 5 mg PO bid was given to all patients at 5 mg PO BID.

The median survival was superior to mitoxantrone only in the 3 week docetaxel arm (18.9 months versus 16.4 months) (p = 0.009). Weekly docetaxel did not result in a statistically significant survival advantage (17.4 months versus 16.4 months, p = 0.36). When compared to the mitoxantrone/prednisone group, the reduction in the risk of death was 24% and 9% for the every 3 week and weekly docetaxel arms, respectively. An updated survival analysis found that more patients survived 3 years when treated with docetaxel either every 3 weeks or weekly (18.6% and 16.6% when compared to mitoxantrone (13.5%).[17] PSA declines of > 50% were significantly higher (45% and 48%) in patients treated on the 3 week and weekly docetaxel groups, respectively, than in the patients treated with mitoxantrone (32%). No significant differences in

TABLE 1. **Docetaxel based phase III trials**

Study	Treatment regimen	Objective measurable response rate (%)	PSA response rate (%)	% with palliative response	Time to progression	Survival (months)
SWOG 9916	Docetaxel/estramustine	17	50	17*	6	18
	Mitoxantrone/prednisone	10	27	11	3	16
TAX 327	Docetaxel (q 3 wks)/prednisone	12*	45	35	7.9*	18.9
	Docetaxel (q wk)/prednisone	8*	48	31	8.2*	17.4
	Mitoxantrone/prednisone	7*	32	22	7.8*	16.5

*did not reach statistical significance

objective response rates were observed in the three treatment arms. Docetaxel therapy was associated with superior palliation of bone pain (33% and 31% in the docetaxel every 3 weeks and weekly regimens as compared to 21% in the mitoxantrone group). Quality-of-life, in general, when using the FACT-P instrument was significantly better in the docetaxel groups as compared to the mitoxantrone group.

Neutropenia was more frequent in the Q3 week docetaxel group (32% compared to 21.7% in the mitoxantrone group). Grade 3 and 4 neutropenia occurred in 3% of patients in the docetaxel Q3 week group, with 2.7% experiencing febrile neutropenia. Neuropathy and alopecia were also more frequent in the docetaxel arms; however the patterns of toxicity were not significantly different between the docetaxel and mitoxantrone groups.

SWOG lead an intergroup study comparing docetaxel/estramustine to mitoxantrone/prednisone.[18] Men randomized to the experimental arm received estramustine at 280 mg PO tid on days 1-5, docetaxel at 60 mg/m^2 IV on day 2 every 21 days, and dexamethasone 60 mg PO in 3 divided doses prior to docetaxel. In contrast to TAX 327, patients did not receive prednisone. Men randomized to the control mitoxantrone arm received mitoxantrone at the same dosage and schedule as in TAX 327. Dose escalation to docetaxel 70 mg/m^2 or mitoxantrone 14 mg/m^2 was permitted for those patients who did not experience grade 3 or 4 toxicity in the first cycle of therapy. Docetaxel combined with estramustine improved median survival (17.5 months compared to 15.6 months, $p = 0.01$), progression-free survival (6.3 months compared to 3.2 months, $p < 0.001$). A greater percentage of patients demonstrated a > 50% PSA decline (50% as compared with 27%, $p < 0.0001$) with docetaxel/estramustine than mitoxantrone/prednisone. A trend towards an improved rate of objective responses in measurable soft tissue disease was noted in favor of Q 3 week docetaxel (17% versus 11%, $p = 0.030$). In addition, palliation of bone pain was not found to be statistically different in the two arms. Overall, the relative risk of death was reduced by 20% with docetaxel and estramustine as compared to mitoxantrone and prednisone (HR for death, 0.80; 95% CI: 0.67-0.97).

Grade 3 and 4 toxicities was reported at higher rates in the docetaxel prednisone arm compared to mitoxantrone/prednisone. The incidence of grade 3 or 4 cardiovascular (15% versus 7%, $p = 0.001$), neurological (7% versus 2%, $p = 0.001$), neutropenic fever (5% versus 2%, $p < 0.001$), gastrointestinal (20% versus 5%, $p < 0.001$), and metabolic disturbances (6% versus 1%, $p < 0.001$) were increased in the experimental arm. However, there was not a higher rate of discontinuation from the study and there was no increase in toxic deaths in the docetaxel/estramustine arm. Prophylactic anticoagulation with Coumadin and aspirin was added to the experimental arm approximately half way through the trial. A post-hoc analysis of toxicity revealed that anticoagulation decreased the rate of cardiac ischemia but not the rate of thrombosis. However, the evaluation of the use of anticoagulation is limited as the trial was not designed to detect a difference in vascular events for patients using anticoagulation as compared to those who did not receive Coumadin and aspirin.

Docetaxel based investigational therapies

A number of novel agents have been investigated for combination with docetaxel in an attempt to improve survival and response in patients with CRPC. The results with docetaxel-based combination therapy have been disappointing. Although serum VEGF levels correlate inversely with survival, antiangiogenesis agents (bevacizumab,[19] aflibercept,[20] lenalidomide,) combined with docetaxel/prednisone have not been a therapeutic advance. Combinations of bone targeted agent such as atrasentan,[21] dasatinib,[22] and ZD4054[23] with docetaxel have also had disappointing results. Vitamin D (calcitriol, DN-101 combined with weekly docetaxel also demonstrates no survival advantage over docetaxel/prednisone.[24] Reasons for the failure of combination therapy include marginal activity of the agents that were combined with docetaxel, as well as dose reduction of docetaxel due to overlapping toxicities.

Cabazitaxel

Granted fast track designation in November of 2009, cabazitaxel combined with prednisone was approved by the FDA in June 2010 for the treatment of men who had previously received a docetaxel-based regimen for CRPC. Cabazitaxel is the third cytotoxic agent to be approved by the FDA for castration resistant disease, and the second to demonstrate a survival benefit over mitoxantrone combined with prednisone.

Mechanism of action

Similar in structure and antitumor mechanism to paclitaxel and docetaxel, cabazitaxel is a novel second-generation, semisynthetic taxane that induces cell

death by microtubule stabilization through inhibition of disassembly. Cabazitaxel binds the N-terminal amino acids of the beta-tubulin subunit, and promotes stabilization of microtubules and the mitotic spindle. In addition to activity against paclitaxel and docetaxel sensitive human cervical, breast, and leukemia and prostate cancer cell lines, cabazitaxel demonstrates activity in taxane resistant cell lines.[25] The explanation for this pattern of activity stems from cabazitaxel's effect on the efflux pump of p-glycoprotein, known to be responsible for the multidrug resistance phenotype. Expressed in a variety of human tumors including prostate cancer, p-glycoprotein is responsible for the adenosine-5′-triphosphate (ATP) dependent extrusion of natural product chemotherapeutic agents such as doxorubicin, vinca alkaloids, as well as paclitaxel and docetaxel. The extra methyl groups found on cabazitaxel are more effective against the ATP dependent efflux pump of p-glycoprotein than similarly placed hydrol groups on docetaxel and paclitaxel. This phenomenon may also be responsible for the disproportional increase CNS accumulation of cabazitaxel with increasing plasma concentrations, demonstrated in rodent models; p-glycoprotein is known to be expressed in the capillary endothelium of the brain and may be responsible for the blood-brain barrier.[26]

Phase I study of cabazitaxel

Mita et al conducted a phase 1 study in 25 patients with chemotherapy refractory solid tumors. Cabazitaxel was administered at four dose levels (10, 15, 20, and 25 mg/m^2) as an intravenous (IV) infusion every 3 weeks. Of the eight CRPC patients entered on the trial, two, previously treated with mitoxantrone and docetaxel, demonstrated partial responses in soft tissue lesions to 15 mg/m^2 and 25 mg/m^2, of cabazitaxel, respectively. Both also manifested > 50% declines in PSA. A third prostate cancer patient demonstrated a minor response. Neutropenia was the major dose limiting toxicity observed, with two patients demonstrating prolonged grade 4 neutropenia at 25 mg/m^2, and another demonstrating febrile neutropenia at the same dose level.[27] In contrast to patients treated with docetaxel, fluid retention was not observed with cabazitaxel treatment. The commonest non-hematologic toxicities observed were diarrhea (52%), nausea (40%), and vomiting (16%). The authors concluded that 20 mg/m^2 of cabazitaxel administered every 3 weeks as the recommended phase II dose. It is to be noted that prophylactic granulocyte colony stimulating factor (GCSF) was not administered.

Phase III studies of cabazitaxel in docetaxel pretreated CRPC patients

The activity of cabazitaxel demonstrated against taxane resistant cell lines, as well as the responses observed in phase I lead investigators to study cabazitaxel in men with castration resistant prostate cancer previously treated with docetaxel. The TROPIC trial randomized 755 men to either cabazitaxel 25 mg/m^2 Q 3 weeks or mitoxantrone 12 mg/m^2 Q 3 weeks. Prednisone 5 mg PO BID was administered in both arms.[28] All patients were required to have progressive disease as evidenced by RECIST criteria or two consecutive rising PSAs at least 1 week apart in patients with non-measurable disease. The median age of patients entered in the metastatic study was 68. A median dosage of 529.2 mg/m^2 and 576.6 mg/m^2 of docetaxel were administered in the cabazitaxel and mitoxantrone/prednisone arms, respectively. Two or more cytotoxic regimens were previously administered to 29% and 31% of the patients entered on the mitoxantrone and cabazitaxel arms, respectively. Nearly half of the patients entered in the trial had symptomatic bone pain, with 25% of patients demonstrating visceral metastases.

After a median follow up of 12.5 months, a 3.1 month improvement in median survival was noted in favor of cabazitaxel treatment, with a hazard ratio of 0.7. At a median follow up of 25.5 months, 15.9% of the cabazitaxel patients survived > 2 years compared to 8.2% of patients treated with mitoxantrone. A subgroup analysis demonstrated that the survival benefit of cabazitaxel over mitoxantrone was maintained in patients who discontinued docetaxel for disease progression compared to those who stopped docetaxel due to toxicity, completion of 10 cycles of treatment, or for other reasons.[19] Although patient selection may play a role, the median survival from the time of the first docetaxel dose in the cabazitaxel group was 29 months (95% CI 27-31) versus 25 months (95% CI 23-28) in the mitoxantrone group. PSA declines of > 50% and objective response rates were superior (39.2% and 14.4%) in the cabazitaxel arm when compared to the mitoxantrone arm (17.8% and 4.4%). The palliation rates using the PPI, were similar in both arms.

Neutropenia was the most commonly encountered toxicity, with grade 3 or higher events occurring in 82% of patients treated with cabazitaxel. Febrile neutropenia was observed in 8% of patients. The prevalence of cabazitaxel induced neutropenia increases with age, and was observed at a 6.6% higher rate in patients over the age of 65. Grade 3 diarrhea was observed in 6% of patients on the cabazitaxel arm compared to < 1% of patients on

TABLE 2. **Common toxicities of docetaxel and cabazitaxel and their management**

Drug	Dose/schedule	Toxicity	Management
Docetaxel Contraindications: Baseline neutrophil count less than 1500 cells/μL, a history of severe hypersensitivity reactions to docetaxel or polysorbate 80, severe hepatic dysfunction (bilirubin >Upper limit of normal (ULN), SGOT and/or SGPT >1.5XULN concomitant with alkaline phosphatase >2.5XULN	75 mg/m^2 Q 3 weeks	Neutropenia	Per ASCO guidelines, risk of febrile neutropenia <20%, use Colony Stimulating Factors (GCSF, GmCSF) based on age, medical condition, history, disease characteristics. Monitor CBC at least weekly
		Fluid retention	Prophylactic administration of steroids, monitor with daily weights, diuretics as needed
		Hypersensitivity reactions	Corticosteroids, antihistamines, H2 antagonists
		Neuropathy	No standard treatment
Cabazitaxel Contraindications: Baseline neutrophil count less than 1500 cells/μL, a history of severe hypersensitivity reactions to docetaxel or polysorbate 80	25 mg/m^2 Q 3 weeks	Neutropenia	GCSF prophylaxis recommended for age > 65, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation, poor nutritional status, other comorbidities. Monitor CBC at least weekly
		Diarrhea	Hydration, treat with antidiarrheals (loperamide). If ≥ grade 3, dosage should be modified
		Hypersensitivity reactions	Corticosteroids, antihistamines, H2 antagonists

the mitoxantrone arm. As with neutropenia, diarrhea was more frequently observed in patients over the age of 75. Diarrhea also was observed at a 8.6% higher rate in patients who had a prior history of radiation therapy. A higher rate of death due to adverse events was noted in patients treated on the cabazitaxel/prednisone arm when compared to mitoxantrone/prednisone. Of the 18 patients on the cabazitaxel arm who died of adverse events, 7 patients died of neutropenic sepsis, in contrast to 1 patient on the mitoxantrone arm. It is to be noted that prophylactic colony stimulating factors were not administered during the first cycle of therapy, which could possibly reduce the risk of neutropenic death. This pattern of toxicity has lead the FDA to recommend administration of prophylactic growth factors in patients treated with cabazitaxel who are older than 65, have had extensive prior radiation, poor nutrition, previous febrile neutropenia, poor performance status or other serious comorbidities. In a report of a global early access program performed in Italy, CRPC patients treated with six cycles of cabazitaxel experienced neutropenia (33.9%), leukopenia (15.6%), anemia (6%), and asthenia.[29] Table 2 shows common toxicities of docetaxel and cabazitaxel and their management.

Two relevant questions regarding sequencing of cabazitaxel and dosage are being answered by randomized clinical trials. Given cabazitaxel's efficacy in docetaxel pretreated patients, it would be logical to evaluate cabazitaxel as front line chemotherapy in men with castration resistant prostate cancer. An international randomized trial of docetaxel combined with prednisone versus cabazitaxel (20 mg/m^2 or 25 mg/m^2)/prednisone is underway, clinical trials.gov NCT01308567. To further define the optional dose, a second study is randomizing patients to either 20 mg/m^2 or 25 mg/m^2 of cabazitaxel, clinical trials.gov NCT01308580.

Sequencing of treatments

With the recent approvals of abiraterone,[30] radium 223,[31] sipuleucel T[32] in the pre-docetaxel space, given the relative lack of toxicity of the aforementioned treatments, chemotherapy potentially could be administered later in the course of disease. It is unclear whether administration of any of these agents before either docetaxel or cabazitaxel affects efficacy and toxicity of these cytotoxic agents. Retrospective studies have been performed in small, select groups of patients and are difficult to apply to individual treatment decisions. For example, the preclinical observation that docetaxel may actually have cross resistance with hormonal agents due to docetaxel inhibition of androgen receptor translocation theoretically could make taxanes less effective after administration of abiraterone or enzalutamide.[33,34] Pond et al found that patients previously treated with ketoconazole/hydrocortisone in a randomized trial of docetaxel+/- AT-101, a novel bcl-2 inhibitor, trended towards bursting overall survival, objective response rates, and PSA declines compared to those patients who had not received prior ketoconazole/hydrocortisone.[35] In a retrospective evaluation of 35 patients who received docetaxel after abiraterone treatment, the median survival was 12.5 months, significantly lower than what was observed in TAX 327. Patients refractory to abiraterone were also refractory to docetaxel. In a small subgroup of patients treated with cabazitaxel after abiraterone alone, abiraterone followed by enzalutamide, or in enzalutamide alone, 16/41(39%) of patients demonstrated a > 50% PSA decline, with a median survival of 15.8 months.[36] Clearly, prospective randomized trials are needed, utilizing biomarkers, to determine the optimal sequence of these agents for both survival and toxicity.

Conclusions

Both docetaxel and cabazitaxel have antitumor activity in chemotherapy naïve and chemotherapy pre-treated patients, respectively. Combination therapy with docetaxel has not resulted in increased survival. Although randomized trials are currently underway to define which of these two agents should be administered as front line therapy, the optional sequences of these agents with newer agents such as abiraterone, enzalutamide and radium 223 have yet to be defined.

Disclosure

Dr. Daniel P. Petrylak has consulted for Bayer, Bellicum, Dendreon, Sanofi Aventis, Johnson and Johnson, Exelixis, Ferring, Millineum, Medivation and Pfizer. He has also received grant support from Oncogenix, Progenies, Johnson and Johnson, Millineum, Celgene and Dendreon. □

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer Statistics, 2014. *CA Cancer J Clin* 2014;64(1):9-29.
2. Crawford ED, Goodman P, Blumenstein B. Combined androgen blockade: leuprolide and flutamide versus leuprolide and placebo. *Semin Urol* 1990;8(3):154-158.
3. Yagoda A, Petrylak D. Cytotoxic chemotherapy for advanced hormone-resistant prostate cancer. *Cancer* 1993;71(3 Suppl): 1098-1109.
4. Eisenberger MA, Simon R, O'Dwyer PJ, Wittes RE, Friedman MA. A reevaluation of nonhormonal cytotoxic chemotherapy in the treatment of prostatic carcinoma. *J Clin Oncol* 1985;3(6): 827-841.
5. 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(6):1756-1764.
6. Kantoff PW, Halabi S, Conaway M et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. *J Clin Oncol* 1999;17(8):2506-2513.
7. Berry W, Dakhil S, Modiano M, Gregurich M, Asmar L. Phase III study of mitoxantrone plus low dose prednisone versus low dose prednisone alone in patients with asymptomatic hormone refractory prostate cancer. *J Urol* 2002;168(6):2439-2443.
8. Bissery MC, Guenard D, Gueritte-Voegelein F, Lavelle F. Experimental antitumor activity of taxotere (RP 56976, NSC 628503), a taxol analogue. *Cancer Res* 1991;51(18):4845-4852.
9. Haldar S, Basu A, Croce CM. Bcl2 is the guardian of microtubule integrity. *Cancer Res* 1997;57(2):229-233.
10. Kreis W, Budman DR, Calabro A. Unique synergism or antagonism of combinations of chemotherapeutic and hormonal agents in human prostate cancer cell lines. *Br J Urol* 1997;79(2):196-202.
11. Budman DR, Calabro A, Kreis W. Synergistic and antagonistic combinations of drugs in human prostate cancer cell lines in vitro. *Anticancer Drugs* 2002;13(10):1011-1016.
12. Picus J, Schultz M. Docetaxel (Taxotere) as monotherapy in the treatment of hormone-refractory prostate cancer: preliminary results. *Semin Oncol* 1999;26(5 Suppl 17):14-18.
13. Petrylak DP, Macarthur R, O'Connor J et al. Phase I/II studies of docetaxel (Taxotere) combined with estramustine in men with hormone-refractory prostate cancer. *Semin Oncol* 1999;26 (5 Suppl 17):28-33.
14. Petrylak DP, Macarthur RB, O'Connor J et al. Phase I trial of docetaxel with estramustine in androgen-independent prostate cancer. *J Clin Oncol* 1999;17(3):958-967.
15. Kreis W, Budman DR, Fetten J, Gonzales AL, Barile B, Vinciguerra V. Phase I trial of the combination of daily estramustine phosphate and intermittent docetaxel in patients with metastatic hormone refractory prostate carcinoma. *Ann Oncol* 1999;10(1):33-38.

16. 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(15):1502-1512.
17. Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol* 2008;26(2):242-245.
18. Petrylak DP, Tangen CM, Hussain MH et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004;351(15): 1513-1520.
19. Kelly WK, Halabi S, Carducci M et al. Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. *J Clin Oncol* 2012;30(13):1534-1540.
20. Tannock IF, Fizazi K, Ivanov S et al. Aflibercept versus placebo in combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): a phase 3, double-blind randomised trial. *Lancet Oncol* 2013;14(8):760-768.
21. Quinn DI, Tangen CM, Hussain M et al. Docetaxel and atrasentan versus docetaxel and placebo for men with advanced castration-resistant prostate cancer (SWOG S0421): a randomised phase 3 trial. *Lancet Oncol* 2013;14(9):893-900.
22. Araujo JC, Mathew P, Armstrong AJ et al. Dasatinib combined with docetaxel for castration-resistant prostate cancer: results from a phase 1-2 study. *Cancer* 2012;118(1):63-71.
23. Fizazi KS, Higano CS, Nelson JB et al. Phase III, randomized, placebo-controlled study of docetaxel in combination with zibotentan in patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 2013;31(14):1740-1747.
24. 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. *J Clin Oncol* 2011;29(16):2191-2198.
25. Vrignaud P, Semiond D, Lejeune P et al. Preclinical antitumor activity of cabazitaxel, a semisynthetic taxane active in taxane-resistant tumors. *Clin Cancer Res* 2013;19(11):2973-2983.
26. Bissery MC, Bouchard H, Riou JF et al. Preclinical evaluation of TXD258, a new taxoid. Proceeding of the 91st Annual Meeting of the American Association for Cancer Research. 2000: Abstract 1364.
27. Mita AC, Figlin R, Mita MM. Cabazitaxel: more than a new taxane for metastatic castrate-resistant prostate cancer? *Clin Cancer Res* 2012;18(24):6574-6579.
28. 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. *Lancet* 2010;376(9747):1147-1154.
29. Bracarda S, Gernone A, Gasparro D et al. Real-world cabazitaxel safety: the Italian early-access program in metastatic castration-resistant prostate cancer. *Future Oncol* 2013 Dec 3. Epub ahead of print.
30. Basch E, Autio K, Ryan CJ et al. Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial. *Lancet Oncol* 2013;14(12):1193-1199.
31. Parker C, Nilsson S, Heinrich D et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013; 369(3):213-223.
32. Kantoff PW, Higano CS, Shore ND et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363(5):411-422.
33. Kirby BJ, Jodari M, Loftus MS et al. Functional characterization of circulating tumor cells with a prostate-cancer-specific microfluidic device. *PloS One* 2012;7(4):e35976.
34. Kuroda K, Liu H, Kim S, Guo M, Navarro V, Bander NH. Docetaxel down-regulates the expression of androgen receptor and prostate-specific antigen but not prostate-specific membrane antigen in prostate cancer cell lines: implications for PSA surrogacy. *Prostate* 20091;69(14):1579-1585.
35. Pond GR, Armstrong AJ, Galsky MD, Wood BA, Leopold L, Sonpavde G. Efficacy of docetaxel-based chemotherapy following ketoconazole in metastatic castration-resistant prostate cancer: implications for prior therapy in clinical trials. *Urol Oncol* 2013;31(8):1457-1463.
36. Pezaro CJ, Omlin AG, Altavilla A et al. Activity of cabazitaxel in castration-resistant prostate cancer progressing after docetaxel and next-generation endocrine agents. *Eur Urol* 2013 Dec 17. Epub ahead of print.