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CONSISE REVIEW

Management Options in Advanced Prostate Cancer: What is the Role for Sipuleucel-T?

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Abstract: Most prostate cancer-related deaths occur in patients with castration-resistant prostate cancer (CRPC). Until recently, only therapy with docetaxel and prednisone has been shown to prolong survival in men with metastatic CRPC. With the United States Food and Drug Administration (US FDA) approvals of sipuleucel-T, cabazitaxel, and abiraterone acetate, all based on improvement in overall survival, the landscape for management of men with metastatic CRPC has dramatically changed. In this review we will discuss the pivotal clinical trial data leading to these approvals, with particular focus on the unique indication for sipuleucel-T and the implications for optimal management and sequencing of treatment in this patient population.

Keywords: Castration-resistant prostate cancer, sipuleucel-T, chemotherapy, abiraterone acetate, cabazitaxel

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Introduction

Prostate cancer is the most common non-skin malignancy and the second leading cause of cancer death in men in the United States.[1] Surgery and radiation are effective therapies for localized prostate cancer, but prostate cancer will recur in 20%–40% of these patients after local therapy.[2] Androgen deprivation therapy (ADT) stabilizes the disease in most patients, however, over time patients will develop castration-resistant prostate cancer (CRPC). Until recently, available therapeutic options for these patients have been limited to off-label use of secondary hormonal manipulations or docetaxel with prednisone, which demonstrated the only improvement in median survival for this population.[3,4] The landscape changed dramatically in 2010 with the U.S. FDA approval of the autologous cellular immunotherapy sipuleucel-T (PROVENGE®; Dendreon Corp. Seattle, WA, USA) for the treatment of men with asymptomatic or minimally symptomatic metastatic CRPC.[5] Shortly thereafter, cabazitaxel/prednisone was approved by the FDA for the treatment of men with metastatic CRPC previously treated with docetaxel chemotherapy.[6] Both sipuleucel-T and cabazitaxel/prednisone were shown to further extend median overall survival. Most recently, abiraterone acetate/prednisone, an oral CYP17 inhibitor of adrenal steroid synthesis, has also been shown to improve survival in patients who progress on taxane-based chemotherapy and is now U.S. FDA approved in the post-docetaxel setting for men with CRPC.[7] The relatively sudden increase in treatment options for men with metastatic CRPC is a benefit for patients but leaves open to interpretation for practitioners the best strategy and sequence of therapies in this disease setting. With this in mind, we have reviewed the data regarding these therapeutic options with particular focus on the emerging strategies for incorporating sipuleucel-T into this changing landscape.

Systemic Therapy in Metastatic CRPC

Historically, the role of chemotherapy in metastatic prostate cancer was limited to symptom palliation with the use of mitoxantrone and prednisone.[8,9] In 2004, the TAX327 study showed that treatment with docetaxel and prednisone prolonged overall survival compared to mitoxantrone and prednisone in metastatic CRPC patients.[4] Patients treated with docetaxel and prednisone also had improved palliation of disease-related symptoms, compared to those receiving treatment with prednisone alone. Similarly, the SWOG9916 trial showed a significant overall and progression-free survival benefit in patients receiving docetaxel and estramustine versus those receiving mitoxantrone and prednisone, with the relative risk for death 20% lower in patients receiving docetaxel-based therapy (hazard ratio (HR) 0.80; 95% confidence interval (CI) 0.67–0.97).[3]

Docetaxel/prednisone was the only approved chemotherapeutic regimen that improved median survival in men with metastatic CRPC until data was reported on the novel taxane, cabazitaxel, in 2010.The TROPIC study was a randomized, phase 3 study of 755 men which examined the effect on survival of cabazitaxel plus prednisone versus mitoxantrone plus prednisone in patients who had progressed on docetaxel-based chemotherapy. Treatment with cabazitaxel/prednisone resulted in an improvement in median overall survival by 2.8 months with a 30% reduced risk of death (HR 0.7, 95% CI 0.59–0.83).[6] This led to U.S. FDA approval of cabazitaxel plus prednisone for patients with metastatic CRPC previously treated with docetaxel and prednisone.

At the European Society for Medical Oncology meeting in late 2010, survival data from a pre-planned interim analysis of the international phase 3 Cougar 301 study of abiraterone acetate and prednisone versus placebo and prednisone was presented. Nearly 1200 patients with metastatic CRPC progressing after docetaxel-based chemotherapy were randomized 2:1 to receive abiraterone acetate and prednisone or placebo and prednisone; the primary endpoint was overall survival. Treatment with abiraterone/prednisone led to a 35% reduction in the risk of death (HR 0.65, 95% CI 0.54–0.77), with an improvement in survival of 3.9 months over placebo/prednisone.[7] Updated survival data after median follow-up of 20.2 months showed an even greater survival benefit in the abiraterone/prednisone arm of 4.6 months over placebo/prednisone (HR 0.74, $P < 0.001$).[10] Furthermore, improvement in the abiraterone/prednisone arm was also seen in time to progression, radiographic progression-free survival, and prostate-specific antigen (PSA) response,[7] leading to the April 2011 U.S. FDA-approval of abiraterone acetate and prednisone in the post-docetaxel setting. An ongoing phase 3 trial of abiraterone acetate with prednisone in the pre-docetaxel

setting is evaluating the earlier use of this active agent in men with metastatic CRPC.

The recent approvals of sipuleucel-T, cabazitaxel/prednisone, and abiraterone/prednisone for the treatment of patients with metastatic prostate cancer have significantly changed the disease landscape. The newly approved agents for the treatment of advanced prostate cancer are summarized in Table 1. How best to incorporate immunotherapy, chemotherapy, and further hormonal therapy into the treatment paradigm of patients with metastatic CRPC remains unclear, especially given that prednisone is a component of therapy with abiraterone, docetaxel, and cabazitaxel but is not recommended during sipuleucel-T therapy due to its immunosuppressive properties. While docetaxel-based therapy has an established treatment paradigm and cabazitaxel and abiraterone were both reported in studies following docetaxel-based chemotherapy, the incorporation of sipuleucel-T in some respects represents the greatest challenge, based on its novel mechanism of action, limited response profile, unique FDA label, access, and cost. We discuss these issues and how they may shape the current and future use of this new treatment.

Sipuleucel-T

Sipuleucel-T is a therapeutic vaccine in which autologous antigen-presenting cells are activated by exposure to a recombinant antigen called PA2024. PA2024 is a chimeric protein containing the tumor-associated antigen prostatic acid phosphatase together with granulocyte-macrophage colony-stimulating factor to activate the immune cells. Therapy with sipuleucel-T involves leukapheresis, during which peripheral blood mononuclear cells containing antigen-presenting cells are collected and cultured ex vivo at a designed facility for approximately 36 hours with the PA2024 antigen. The cell product is then delivered to the treatment site, and the primed cells are infused into the same patient from which they were collected. Each round of therapy consists of leukapheresis followed by intravenous infusion of the primed antigen-presenting cells, and treatment is given every two weeks for a total of three treatments. The mechanism of action, therefore, is to engage the patient's immune response to attack the prostate cancer cells specifically.

Two randomized, multicenter, double-blind phase III trials compared sipuleucel-T with placebo in men with metastatic CRPC. The first trial, known as D9901, enrolled 127 patients and failed to meet its primary endpoint of progression-free survival (PFS), with time to progression of 11.7 weeks for the sipuleucel-T arm and 10 weeks for the placebo arm ($P = 0.52$).[11] As a result, the second trial (D9902) was closed after only 98 patients enrolled.[12] However, when the overall survival data for D9901 became available and showed a statistically-significant 4-month improvement in the sipuleucel-T arm, the second trial was split into two parts: D9902 A, which included the 98 patients already enrolled, and D9902B, which was revised to make overall survival the primary endpoint.

D9902B became known as the IMPACT (Immunotherapy for Prostate Adeno Carcinoma Treatment) trial and enrolled 512 men with metastatic CRPC with a life expectancy of at least 6 months.[5] Initially only men with asymptomatic disease and a Gleason score ≤ 7 were enrolled; however, once the survival benefit from D9901 was shown to be independent of histologic grade, the study was amended to include asymptomatic or minimally symptomatic patients

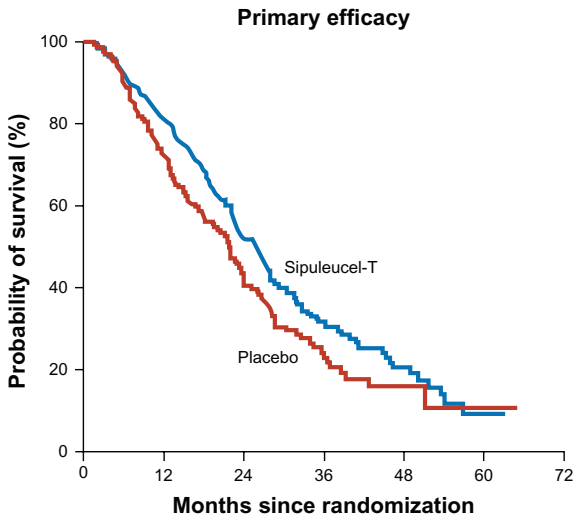
Table 1. Newly approved agents in CRPC.

Agent	Mechanism of action	Indication	PFS benefit	OS benefit
Sipuleucel-T (PROVENGE®)	Autologous cellular immunotherapy (PAP-directed)	Asymptomatic to minimally symtomatic metastatic CRPC	none	4.1 months vs. placebo (HR 0.78, 95% CI 0.61–0.98)[5]
Cabazitaxel (Jevtana®)	Microtubule inhibition	Metastatic CRPC, post-docetaxel	1.4 months	2.8 months vs. mitoxantrone (HR 0.70, 95% CI 0.59–0.83)[6]
Abiraterone (Zytiga®)	CYP17a inhibitor of adrenal and autocrine/paracrine androgen biosynthesis	Metastatic CPRC, post-docetaxel	2.0 months	4.6 months vs. prednisone (HR 0.74, 95% CI 0.64–0.86)[10]

Abbreviation: PAP, Prostatic Acid Phosphatase.

with any Gleason score. Additionally, patients were required to have a PSA level of ≥5 ng/mL, testosterone of ≤50 ng/dL, and evidence of progressive disease. Patients with an ECOG performance status of ≥2, visceral metastases, pathologic long-bone fractures, or those receiving two or more prior chemotherapy regimens were excluded. Patients were randomly assigned in a 2:1 ratio to receive either sipuleucel-T or placebo, in which the autologous cells were not exposed to the chimeric protein. The primary endpoint was overall survival, with time to disease progression as the secondary endpoint.

The IMPACT study conclusively confirmed the overall survival advantage previously seen for patients receiving sipuleucel-T vs. placebo. Patients in the sipuleucel-T-treatment arm had a 22% reduction in risk of death (HR 0.78, 95% CI 0.61–0.98; $P = 0.032$) and a 4.1-month improvement in median survival (25.8 vs. 21.7 months), as illustrated in Figure 1. The 36-month survival probability was 32.1% for sipuleucel-T versus 23% for control. Similar to the prior studies, no difference in PFS was noted between the two arms, with progression documented at 14.6 weeks in the sipuleucel-T arm and at 14.4 weeks in the placebo arm. Likewise, there was no significant difference in PSA response or decrease in tumor size by imaging, and given that men were asymptomatic to minimally symptomatic, no palliative benefit or



No. at risk						
Sipuleucel-T	341	274	129	49	14	1
Placebo	171	123	55	19	4	1

Figure 1. Overall survival benefit of 4.1 months ($P = 0.03$) with sipuleucel-T treatment.
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delay in pain onset or time to chemotherapy was noted with sipuleucel-T.[5] The fact that a PFS advantage was not seen in the context of this novel immune therapy is consistent with other immunotherapies, such as ipilimumab in melanoma.[13] Recent guidelines for interpreting the benefits of immunotherapies in cancer have been published, which may better account for delayed onset treatment effects that are not well captured using current methods.[14]

Integrated safety results from more than 600 patients from four randomized, double-blind sipuleucel-T studies, three studies in CRPC and one in androgen-dependent prostate cancer, showed that the most common side-effects associated with sipuleucel-T were chills, pyrexia, headache, and myalgia. Most of the reactions occurred the day after infusion, were mild or moderate in severity, and resolved within 2 days. Side effects were slightly more common after the second and third infusions than the first infusion.[15]

More than half of patients in the placebo group of the IMPACT study (109 of 171 patients) crossed over to receive APC8015F as part of an open-label salvage protocol. APC8015F is made from the cryo preserved leukophoresis product and is otherwise manufactured and administered identically to sipuleucel-T. A recent combined analysis of the patients in the control arms of the three randomized trials of sipuleucel-T in metastatic CRPC aimed to assess the efficacy of treatment with APC8015F. APC8015F-treated subjects (n = 155) had improved survival relative to untreated controls (n = 61), with a 48% reduced risk of death (HR = 0.52, 95% CI 0.37–0.73). When adjusted for age, PSA, LDH, and docetaxel treatment after randomization the significant survival benefit remained (HR 0.56, 95% CI 0.4–0.8).[16] Although confounded by unmeasured factors related to the non-random use of the frozen product, this analysis suggests that treatment with APC8015F was not associated with a worse outcome and may prolong overall survival. If so, the survival benefit noted in the sipuleucel-T versus placebo arms of the trials may actually be an underestimate compared to a true no-treatment control.

The implications of treatment with sipuleucel-T on current practice are significant. Sipuleucel-T is FDA-approved for asymptomatic or minimally symptomatic men with metastatic disease, which consequently requires more aggressive screening of men with CRPC for evidence of metastatic disease. Historically, many

patients in the asymptomatic CRPC disease state have been managed conservatively with continued ADT, secondary hormonal manipulations, or expectant management. Active screening of men with asymptomatic non-metastatic CRPC for the development of metastases is therefore increasingly important to identify patients for treatment with sipuleucel-T as well as for bone-targeted therapy.

Asymptomatic and Minimally Symptomatic Metastatic CRPC

The approval of sipuleucel-T for patients with asymptomatic metastatic disease should result in more aggressive screening for the development of metastases. Currently, most patients with biochemical relapse after definitive therapy are treated with androgen deprivation therapy. The majority of these patients will have a PSA response, though eventually the PSA will rise again. There is no standard surveillance method or treatment for patients with a rising PSA despite ADT, and a previous observational study of more than 200 men showed that many of these patients have no evidence of metastatic disease until a median of 30 months.[17] However, a recent study designed to treat non-metastatic CRPC patients with zibotentan versus placebo revealed an unexpectedly high number screening failures, prompting further analysis. Of the more than 1,700 patients screened for metastases by bone scan and CT or MRI, 531 patients (30%) failed screening due to the presence of metastatic disease.[18] This suggests that asymptomatic metastases are common and supports the role of periodic staging studies in men with CRPC, particularly given the expanded treatment options for these men.

Poor risk prognostic factors have been identified to help providers predict metastatic disease progression and survival in men with non-metastatic CRPC. As mentioned above, an observational study of more than 200 men with non-metastatic CRPC revealed a relatively indolent course with median time to metastasis of 30 months. However, in that study, both the PSA and the PSA doubling time (PSA DT) were directly proportional to the time to metastases. Specifically, patients with a PSA level $>$ 24 ng/ml or a PSA DT $<$ 6.3 months developed metastases or death at a median of $<$12 months. Even those patients with PSA levels $>$ 7.7 ng/ml or PSA DT $<$ 18.8 months had a 25%–30% likelihood of developing metastases or death within one year.[14] These data suggest that patients who are started on primary ADT without metastases should be radiographically restaged regularly (perhaps every 4 months as in the study above) for evidence of metastatic disease once they become castration-resistant, if they have a PSA DT $<$ 18 months or a PSA level $>$ 7.7 ng/ml.

Among men with metastatic CRPC, this asymptomatic to minimally symptomatic population has a favorable survival. In the TAX327 study, a good risk population was identified that lacked pain, visceral metastatic disease, significant anemia, and bone scan progression, despite having progressive metastatic CRPC. These men had an expected survival of 23–28 months, and a one year survival rate of 80%–90%.[19] Thus, the use of less toxic therapies such as immunotherapy in this setting, where prolonged survival rather than palliation of symptoms is the primary goal, is quite reasonable.

Regular surveillance for metastatic disease is also crucial for the proper use of bone-targeting therapies such as zoledronic acid or denosumab. The bisphosphonate zoledronic acid is superior to placebo in preventing skeletal-related events (SRE) and prolonging the time to the first SRE, and has been a mainstay of supportive therapy for patients with metastatic CRPC.[20] Denosumab is a humanized monoclonal antibody that binds to RANKL, a protein important for osteoclast function. Zoledronic acid and denosumab were compared in a phase 3 study of men with metastatic CRPC, and both agents were effective in preventing SREs, defined as pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. Compared to zoledronic acid, men receiving denosumab had improved time to first SRE (20.7 vs. 17.1 months, $P = 0.008$), but there was no difference in progression-free or overall survival.[21] On the basis of this and two other large non-inferiority studies, denosumab is U.S. FDA-approved for the prevention of SREs in metastatic prostate and other solid tumors. Therefore, early identification of patients with metastatic disease provides the opportunity to offer bone-targeting therapy to prevent SREs as well as immunotherapy to prolong survival.

Sequencing of Therapy

With the recent approval of multiple new agents for metastatic prostate cancer comes the question of how best to sequence therapy. In the IMPACT study, the

majority of patients received sipuleucel-T prior to treatment with docetaxel/prednisone. In contrast, in the TROPIC study, patients received cabazitaxel/prednisone following progression on docetaxel/prednisone, and a statistically significant survival benefit was demonstrated. Similarly, in Cougar 301, patients received abiraterone/prednisone following progression on docetaxel/prednisone and again demonstrated a statistically significant survival benefit.

There is great interest in using abiraterone/prednisone earlier in the course of disease, as it is an oral regimen that has been well-tolerated. Cougar 302 is currently accruing and is designed to look at giving abiraterone/prednisone early, to the minimally symptomatic metastatic patient, potentially followed by treatment with sipuleucel-T, docetaxel/prednisone, and cabazitaxel/prednisone. However, the current phase III evidence suggests that sipuleucel-T should be given early to asymptomatic or minimally symptomatic CRPC patients, followed by docetaxel/prednisone, followed then by either abiraterone/prednisone or cabazitaxel/prednisone. Ongoing studies will likely further alter the recommended strategy for treatment sequencing. Importantly, not all CRPC patients will qualify for sipuleucel-T based on their symptoms or histologic type of prostate cancer, so no single sequence of treatments will be optimal for all patients.

In the IMPACT study, approximately eighty-five percent of patients treated with sipuleucel-T were chemotherapy-naïve.[5] Due to the time it takes for the patient's anti-tumor response to fully develop, the absolute benefit associated with sipuleucel-T therapy may increase with longer survival; therefore, administering immunotherapy early in CRPC may maximize the efficacy and cost-effectiveness of this treatment. An ongoing phase III study of sipuleucel-T versus placebo in hormone-sensitive, non-metastatic prostate cancer patients will help to address this issue. Also, because the chemotherapeutic agents and abiraterone are administered with concomitant steroid therapy, there is likely benefit to treatment with sipuleucel-T prior to initiation of immunosuppressive medications. To date it is unclear how long it is necessary to wait before starting another treatment following sipuleucel-T; however, there is theoretical concern that immediate subsequent treatment with immunosuppressive agents could impact the mechanism of action of sipuleucel-T.

Low-dose corticosteroids are an integral part of the systemic therapy for metastatic prostate cancer. In part, this is historical, as the anti-inflammatory properties of steroids are known to improve pain and palliate disease symptoms.[22] An early trial of cytotoxic therapy in metastatic CRPC compared mitoxantrone plus prednisone to prednisone alone and found improved palliation with the combined therapy.[8] Most subsequent trials have used mitoxantrone plus prednisone as the control arm; therefore, both docetaxel and cabazitaxel are administered with daily low-dose corticosteroids. Low-dose prednisone is also used with the CYP17 inhibitor abiraterone, based on the drug's effects on the adrenal corticosteroid axis. CYP17 inhibition raises levels of adrenal corticotropic hormone (ACTH), and without exogenous glucocorticoid administration, may cause a syndrome of mineralocorticoid excess including hypertension, fluid retention, and hypokalemia.[23] As a result of multiple agents being administered with corticosteroids, patients with metastatic CRPC may now remain on low-dose steroid therapy for months to years. Chronic steroid therapy is associated with well-documented side effects including hypertension, steroid dependence, peptic ulcer disease, weight gain, glucose intolerance, glaucoma, and risk of infection. Therefore, what was initially intended to be a palliative measure is now given with several different therapies and may have unintended consequences.

Corticosteroids also attenuate the immune response and therefore are not recommended to be given with sipuleucel-T. In the IMPACT study, steroids were not given within 28 days of sipuleucel-T initiation and were not resumed until there was objective evidence of disease progression. The median time to progression was 14 weeks, and given that the therapy itself requires 4 weeks to administer, most patients therefore received subsequent treatment within a few months of completion of sipuleucel-T. Two thirds of patients receiving sipuleucel-T had a measurable antibody response to the immunogen and survival was improved in these patients.[5] It is unclear what effect, if any, subsequent low-dose steroid therapy has on the long-term efficacy of sipuleucel-T and other immunotherapies. There is preclinical evidence that that glucocorticoids may not interfere with the antitumor response of immunotherapy,[24] but this needs to be further studied in prostate cancer patients. No controlled studies of

differential timing of subsequent therapies have been conducted, and treatment decisions after sipuleucel-T are typically made by clinical judgment over the risks and benefits of withholding or starting a new systemic agent. The use of prior sipuleucel-T is one of many factors, including also the rapidity of disease progression, tumor-related symptoms, and patient anxiety, which should be considered when deciding on subsequent systemic agents.

Access to Sipuleucel-T

On-label treatment with sipuleucel-T is currently covered by Medicare and most other large insurance companies; in fact, the Centers of Medicare and Medicaid Services (CMS) released a national coverage decision stating that sipuleucel treatment is 'reasonable and necessary'.[25] However, to this point in time, access to sipuleucel-T has been limited by the restricted number of treatment centers, the production capability of the manufacturing plant, and the logistical limitations of flying the product to areas of the country remotely accessed from the manufacturing facility in New Jersey. The addition of manufacturing facilities in Atlanta and Southern California later this year will alleviate this concern for many, but not all, rural patients. Finally, there remain clinicians who are not convinced of the effectiveness of this therapy, either because of its novel but not yet fully established mechanism of action, or its lack of intermediate endpoint benefit (PFS or PSA response), and therefore are unwilling to treat patients with this life-prolonging therapy.

Conclusion

Treatment with sipuleucel-T therapy improves overall survival without a measurable immediate antitumor effect. The therapy should be given to asymptomatic or minimally symptomatic men with metastatic CRPC, and as such, patients need to be restaged regularly to optimally identify this population. Phase III evidence supports the early use of sipuleucel-T therapy prior to docetaxel/prednisone therapy in most cases. Availability, cost of therapy, physician bias as well as established and emerging alternative treatments remain barriers to care with sipuleucel-T. Future data establishing subpopulations of patients with greater benefit from sipuleucel-T as well as adjuvant immune modulation of this platform are needed to build upon the promising results of today.

Disclosures

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References

1. Jemal A, et al. Cancer statistics, 2010. *CA Cancer J Clin*. 2010;60(5): 277–300.
2. Ward JF, Moul JW. Biochemical recurrence after definitive prostate cancer therapy. Part I: defining and localizing biochemical recurrence of prostate cancer. *Curr Opin Urol*. 2005;15(3):181–6.
3. Petrylak DP, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med*. 2004;351(15):1513–20.
4. Tannock IF, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502–12.
5. Kantoff PW, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363(5):411–22.
6. de Bono J.S, 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):1147–54.
7. de Bono JS, et al. Abiraterone acetate plus low dose prednisone improves survival in patients with metastatic castration resistant prostate cancer who have progressed after docetaxel-based chemotherapy: Results of COU-AA-301, a randomized double-blind placebo-controlled phase III study. ESMO annual meeting, Milan, Italy, 2010(Abstract LBA5).
8. Tannock IF, 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):1756–64.
9. Kantoff PW, 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):2506–13.
10. Scher HI, et al. Evaluation of circulating tumor cell (CTC) enumeration as an efficacy response biomarker of overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC): Planned final analysis (FA) of COU-AA-301, a randomized double-blind, placebo-controlled phase III study of abiraterone acetate (AA) plus low-dose prednisone (P) post docetaxel. *J Clin Oncol*. 2011;29(suppl; abstr LBA4517).
11. Small EJ, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. *J Clin Oncol*. 2006;24(19):3089–94.
12. Higano CS, et al. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. *Cancer*. 2009;115(16):3670–9.

13. Hodi FS, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711–23.
14. Hoos A, et al. Improved endpoints for cancer immunotherapy trials. *J Natl Cancer Inst.* 2010;102(18):1388–97.
15. Hall SJ, Integrated safety results from 4 randomized, double-blind, placebo-controlled studies of sipuleucel-T, in 105th American Urological Association Meeting. 2010: San Francisco, California.
16. George DJ, et al. Subsequent treatment with APC8015F and its effect on survival in the control arm of phase III sipuleucel-t studies. *J Clin Oncol*. 2011;29(suppl 7; abstr 139).
17. Smith MR, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. *J Clin Oncol.* 2005;23(13): 2918–25.
18. Yu EY, Nathan FE, Higano CS. Role of detection of metastatic disease as a leading cause of screening failure in an ongoing phase III trial of zibotentan versus placebo in patients with nonmetastatic castration-resistant prostate cancer (CRPC). *J Clin Oncol*. 2011;29(suppl 7; abstr 135).
19. Armstrong AJ, et al. The development of risk groups in men with metastatic castration-resistant prostate cancer based on risk factors for PSA decline and survival. *Eur J Cancer.* 2010;46(3):517–25.
20. Saad F, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst.* 2002;94(19):1458–68.
21. Fizazi K, 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(9768):813–22.
22. Tannock I, et al. Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. *J Clin Oncol*. 1989;7(5):590–7.
23. Attard G, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *J Clin Oncol*. 2008;26(28):4563–71.
24. Hinrichs CS, et al. Glucocorticoids do not inhibit antitumor activity of activated CD8+ T cells. *J Immunother.* 2005;28(6):517–24.
25. Proposed decision memo for autologous cellular immunotherapy treatment of metastatic prostate cancer (CAG-00422 N), in Centers for Medicare and Medicaid Services. March 30, 2010.

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