

The Changing Landscape of Treatment Options For Metastatic Castrate-Resistant Prostate Cancer

Challenges and Solutions for Physicians and Patients

Carole Alison Chrvala, PhD

INTRODUCTION

Prostate cancer is the most common cancer affecting men in the U.S. It is estimated that 241,740 new cases of prostate cancer will have been diagnosed during 2012, accounting for 29% of incident cancers in males.¹ Age-adjusted and delay-adjusted analyses reveal declines in the incidence of prostate cancer from 183.66 per 100,000 in 2000 to 157.92 per 100,000 in 2008.² Prostate cancer is second to lung cancer as a leading cause of cancer mortality in the U.S., with 28,170 deaths anticipated for 2012.¹ Mortality rates have significantly declined in the previous two decades, from 38.34 per 100,000 in 1990 to 22.93 per 100,000 in 2008,² and the 5-year relative survival rate for all stages of prostate cancer has increased from 66.4% in 1975 to 99.4% in 2003.³

Screening

Screening with the prostate-specific antigen (PSA) serum test is credited with the improved survival rates as a result of earlier detection of asymptomatic, clinically localized prostate cancers. However, prostate cancer screening has been an issue of controversy in the U.S. The most recent update to the 2008 U.S. Preventive Services Task Force guidelines recommends against PSA screening based on moderate or high certainty that it offers no net benefit or that the potential harms outweigh the benefits.⁴

The rationale for this recommendation is a high rate (approximately 80%) of false-positive results using cutoffs for serum PSA levels between 2.5 and 4.0 mcg/L. These false-positive results are often associated with unfavorable psychological effects and additional testing, including one or more biopsies in the following year compared with a negative PSA result.⁴ Prostate biopsies result in pain, fever, bleeding, infection, transient urinary problems, and additional clinical follow-up for about one-third of men.⁴ The updated guidelines are also based on evidence that PSA screening results in overdiagnosis and overtreatment of prostate cancers that are unlikely to become symptomatic.

The task force guidelines considered the magnitude of treatment-related harms to be at least moderate.⁴ However, the newly issued guidelines acknowledge that use of PSA screening has become a usual standard of care, and the decision to start or continue screening should be based on a process of shared decision-making between patients and physicians with a thorough discussion of the potential risks and benefits.⁴

Notably, in a recent survey of 125 primary care physicians, most respondents considered both patient age and estimated

life expectancy when recommending PSA screening;⁵ however, they disagreed on the age at which to discontinue screening. About two-thirds of physicians (66.4%) indicated that it was difficult to assess life expectancy. The respondents also indicated several barriers to discontinuation of PSA screening; 74.4% cited patient expectations to continue yearly PSA tests, with 66.4% noting that it would take more time to explain reasons for not screening, compared with time required to simply continue screening, and 54.0% reported an increased sense of a risk for malpractice if they did not order a PSA test.⁵ These findings suggest that the controversy regarding PSA screening is likely to persist despite the recent update to the task force guidelines.

Prognosis

The most favorable prognosis is associated with low-risk disease, characterized by a PSA value of 10 ng/mL or less, a Gleason score of 6 or less, and clinical stage T1c or T2a.^{6,7} Patients at high risk of recurrence include those with clinically localized stage T3a disease with a Gleason score of 8 to 10 or a PSA level above 20 ng/mL.⁷ Although only 29.8% of men had a diagnosis of low-risk prostate cancer from 1989 to 1992, this rate increased to 45.3% by 2001.⁸ Patients with localized prostate cancer initially have favorable responses to active surveillance or treatment with either radical prostatectomy or radiation therapy. A multicenter longitudinal study of radical prostatectomy (N = 12,677) revealed an overall 12% prostate cancer-specific mortality (PCSM) rate, with a 95% confidence interval (CI) of 9% to 15%. Among patients with low-risk disease, the 15-year PCSM rate was 5% (95% CI, 3–7) compared with 38% (95% CI, 19–56) for men with high-risk disease.⁹

However, it is estimated that 20% to 40% of patients with a diagnosis of high-grade, clinically localized prostate cancer subsequently experience relapse,^{10–12} characterized by rising PSA levels following initial therapy. Furthermore, biochemical recurrence following prostatectomy, defined as a PSA level above 0.2 ng/mL,¹³ may progress to metastatic disease in 30% to 70% of men within 10 years of the initial diagnosis.^{10–12,14–18}

The first-line treatment of patients with symptomatic, advanced-stage or metastatic prostate cancer relies on androgen-deprivation therapy (ADT). ADT can be accomplished by either surgical or medical castration with the continuous or intermittent administration of a luteinizing hormone-releasing hormone (LHRH) agonist with or without antiandrogen therapy.⁷ Although ADT is initially associated with a favorable response for most men, most patients eventually develop castrate-resistant (hormone-refractory) prostate cancer (CRPC). CRPC is characterized by serial increases in serum PSA levels,

Dr. Chrvala is President of Health Matters, Inc., an independent medical writing and research consulting company in Hillsborough, N.C.

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evidence of progression on radiographic evaluation, and the development of symptoms.¹⁹⁻²¹ The clinical course of CRPC is quite diverse; some patients develop nonmetastatic disease, whereas others experience asymptomatic or symptomatic metastatic CRPC.^{19,20}

Multiple mechanisms are thought to promote progression to CRPC, including overexpression of the androgen receptor; mutations in androgen receptors that increase androgen sensitivity; and increased production of local androgens by prostate cells, attributed to the expression of steroidogenic enzymes.^{19,20} Other factors implicated in disease progression include (1) modulation of androgen receptor regulators, including co-activators (e.g., the p160 family of nuclear steroid receptor co-activators and NCOA2), (2) co-repressors (e.g., β -arrestin 2), and (3) the down-regulation of androgen receptor-related co-repressors.^{19,20}

Activation of androgen receptor-independent pathways is also implicated in the development of CRPC, including the PI3K/Akt/mTOR pathway; the Ras/Raf/ERK pathway; and other pathways, such as transforming growth factor (TGF)- β R, Wnt/ β -catenin, Src kinase, and interleukin-6R.^{19,20} Evidence is also emerging to suggest that the processes of tumor cell growth, angiogenesis, and metastasis are related to an interaction between prostate cancer cells and the bone microenvironment.²⁰ Patients at increased risk of progression to metastatic CRPC include those with rapid PSA doubling times and PSA levels above 20 ng/mL.^{14,15,22,23} Notably, the median survival of men with metastatic CRPC is 18 to 24 months.^{21,24,25} This article summarizes the efficacy and safety of newly approved and emerging systemic therapies for metastatic CRPC.

NEWLY APPROVED TREATMENTS

Most patients with metastatic CRPC require aggressive treatment to slow disease progression and to prevent metastasis. Before 2004, chemotherapy for metastatic CRPC did not improve survival, although treatment with mitoxantrone (Novantrone, EMD Serono) and prednisone or hydrocortisone was effective for alleviating pain associated with bone metastases.^{26,27} However, significant advances have been made during the decade in the development of alternative treatments for metastatic CRPC that are safe and effective, with the choice of treatment guided by the presence or absence of symptoms.⁷

Currently, four systemic agents have been shown to improve

overall survival for patients with metastatic CRPC and have received approval by the FDA for this indication: docetaxel (Taxotere, Sanofi), sipuleucel-T (Provenge, Dendreon), cabazitaxel (Jevtana, Sanofi), and abiraterone acetate (Zytiga, Janssen).⁷ Favorable results for other systemic treatments for metastatic CRPC also have been reported and are pending submission to or approval by the FDA.

Docetaxel (Taxotere)

Docetaxel is the most frequently administered therapy for chemotherapy-naïve patients with symptomatic, metastatic CRPC. Approved by the FDA in 2004, docetaxel is a semisynthetic taxane that inhibits microtubular depolymerization and phosphorylates Bcl-2, which leads to cell apoptosis.^{28,29} Two phase 3 trials established the efficacy of docetaxel for the treatment of metastatic CRPC: TAX 327 and SWOG 9916 (Southwest Oncology Group) (Table 1).^{28,30}

The TAX 327 Trial

TAX 327, a non-blinded, international study, enrolled patients with confirmed adenocarcinoma of the prostate gland that had progressed to metastatic disease while they were receiving ADT. Patients were randomly assigned to one of three groups: docetaxel 75 mg/m² every 3 weeks (n = 335), docetaxel 30 mg/m² once weekly (n = 334), or mitoxantrone 12 mg/m² every 3 weeks (n = 337). All three groups also received oral prednisone or prednisolone 5 mg twice daily starting on day 1.

The median duration of follow-up was 20.8 months for patients who received docetaxel every 3 weeks and 20.7 months for those in the other two treatment arms. Median survival time was 18.9 months for docetaxel 75 mg/m², 17.4 months for docetaxel 30 mg/m², and 16.5 months for mitoxantrone. The difference in survival rates between the docetaxel 30-mg/m² group and the placebo group was not statistically significant ($P = 0.36$). However, the hazard ratio (HR) for death in the combined docetaxel groups, compared with mitoxantrone, was 0.83 (95% CI, 0.70–0.99; $P = 0.04$).³⁰

An updated analysis of survival in TAX 327 included follow-up results through March 2007 and confirmed that the docetaxel regimen maintained superior efficacy compared with mitoxantrone.³¹ The median survival rate for patients in the docetaxel 75 mg/m² group was 19.2 months compared with

Table 1 Summary of Primary Endpoints for TAX 327 and Southwest Oncology Group (SWOG) 9916 Trials

Trial	Treatment Group	Death Rate (%)	HR for Survival (95% CI)	Median Survival Duration (Months)
TAX 327 ^a	• Docetaxel 75 mg/m ² every 3 weeks	50.0	0.76 (0.62–0.94)	18.9 (17.0–21.2)*
	• Docetaxel 30 mg/m ² every week	57.0	0.91 (0.75–1.11)	17.4 (15.7–19.0)*
	• Mitoxantrone 12 mg/m ² every 3 weeks	60.0	Reference	16.5 (14.4–18.6)*
SWOG 9916 ^b	• Docetaxel 60–70 mg/m ² estramustine 280 mg, and dexamethasone 60 mg every 3 weeks	64.0	0.80 (0.67–0.97)	17.5
	• Mitoxantrone 12–14 mg/m ² and prednisone 5 mg every 3 weeks	70.0	Reference	15.6

*95% confidence interval.

^aData from Tannock IF, de Wit R, Berry WR et al. *N Engl J Med* 2004;351(15):1502–1512.³⁰

^bData from Petrylak DP, Tangen CM, Hussain MH, et al. *N Engl J Med* 2004;351(15):1513–1520.²⁸

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16.3 months for patients receiving mitoxantrone plus prednisone (HR, 0.79; 95% CI, 0.67–0.93; $P = 0.004$). The difference in median survival between these two groups was 2.9 months; 18.6% of patients receiving docetaxel 75 mg/m² survived at least 3 years, compared with 16.8% of those treated with docetaxel 30 mg/m² and 13.5% of those receiving mitoxantrone plus prednisone.³¹

The SWOG 9916 Trial

In the multicenter SWOG 9916 study, 770 men were randomly assigned to one of two treatment groups; 674 patients met study eligibility criteria, which included adenocarcinoma of the prostate and progressive metastatic disease following ADT.²⁸ A total of 338 patients received estramustine (Emcyt, Pfizer) 280 mg three times daily, 1 hour before or 2 hours following meals on days 1 through 5, plus docetaxel 60 mg/m² preceded by oral dexamethasone 60 mg in three divided doses with the first dose taken the night before docetaxel. Alternatively, patients ($n = 336$) received mitoxantrone 12 mg/m² on day 1 plus prednisone 5 mg twice daily. Both regimens were given in 21-day cycles. The doses of docetaxel and mitoxantrone were increased to 70 mg/m² and 14 mg/m², respectively, if there were no occurrences of grade 3 or 4 adverse events during the first cycle.²⁸

The intention-to-treat (ITT) analysis revealed a median survival of 17.5 months for docetaxel compared with 15.6 months for mitoxantrone and prednisone ($P = 0.02$). The HR for death was 0.80 (95% CI, 0.67–0.97) in favor of docetaxel. The median time to progression was 6.3 months for patients in the docetaxel arm compared with 3.2 months for patients in the mitoxantrone plus prednisone arm ($P < 0.001$).²⁸ The results from TAX 327 and SWOG 9916 led to the FDA's approval of docetaxel in 2004 for the treatment of chemotherapy-naïve patients with metastatic CRPC.²¹

Cabazitaxel (Jevtana)

Cabazitaxel, which was approved for the treatment of metastatic CRPC by the FDA in 2010, is a tubulin-binding taxane that has established efficacy for the treatment of solid tumors that are resistant to docetaxel.^{32,33} An international, multicenter, randomized, open-label, phase 3 trial compared cabazitaxel plus prednisone with mitoxantrone plus prednisone for metastatic CRPC that had progressed following treatment with a docetaxel-based regimen.

Patients received either 21-day cycles of cabazitaxel 25 mg/m² ($n = 378$) or mitoxantrone 12 mg/m² ($n = 377$). Both groups also received prednisone 10 mg.³³ The median follow-up period was 12.8 months. Median overall survival rates were 15.1 months (95% CI, 14.1–16.3) for cabazitaxel and 12.7 months (95% CI, 11.6–13.7) for mitoxantrone. This difference reflected a 30% reduction in relative risk of death for cabazitaxel (HR, 0.70; 95% CI, 0.59–0.83; $P < 0.0001$).

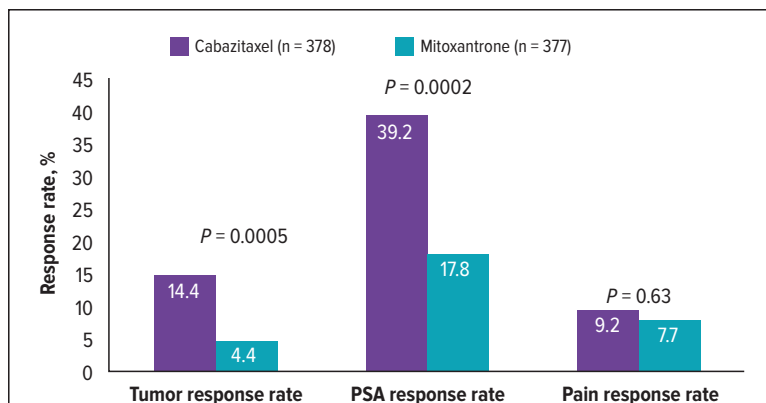


Figure 1 Efficacy of cabazitaxel (Jevtana) versus mitoxantrone (Novantrone) in the treatment of castrate-resistant prostate cancer. PSA = prostate-specific antigen. (Adapted from de Bono JS, Oudard S, Ozguroglu M, et al. *Lancet* 2010;376(9747):1147–1154.³³)

Median progression-free survival also favored cabazitaxel at 2.8 months (95% CI, 2.4–3.0) compared with 1.4 months (95% CI, 1.4–1.7) for mitoxantrone (HR, 0.74; 95% CI, 0.64–0.86; $P < 0.0001$). Additional endpoints regarding rates of tumor response, PSA progression, and pain response are presented in Figure 1 and Table 2.³³

Mortality rates owing to toxicities within 30 days following the last dose of study drug were higher for cabazitaxel (4.9%) than for mitoxantrone (2.4%).³³ The most frequently reported hematological toxicities were as follows:

- neutropenia, grade 3 or higher: 81.7% for cabazitaxel, 58.0% for mitoxantrone
- leukopenia: 68.2% for cabazitaxel, 42.3% for mitoxantrone
- anemia: 10.5% for cabazitaxel, 4.9% for mitoxantrone

Diarrhea (grade 3 or higher) affected 6.2% of cabazitaxel patients and fewer than 1.0% of men receiving mitoxantrone. Rates were comparable for nonhematological toxicities (grade 3 or above) between the two treatment groups.³³

These results underscore the importance of monitoring, prophylactic interventions, and therapy for patients receiving cabazitaxel.³³ Cabazitaxel causes nausea, vomiting, and severe diarrhea in some patients.³² Recommended supportive care

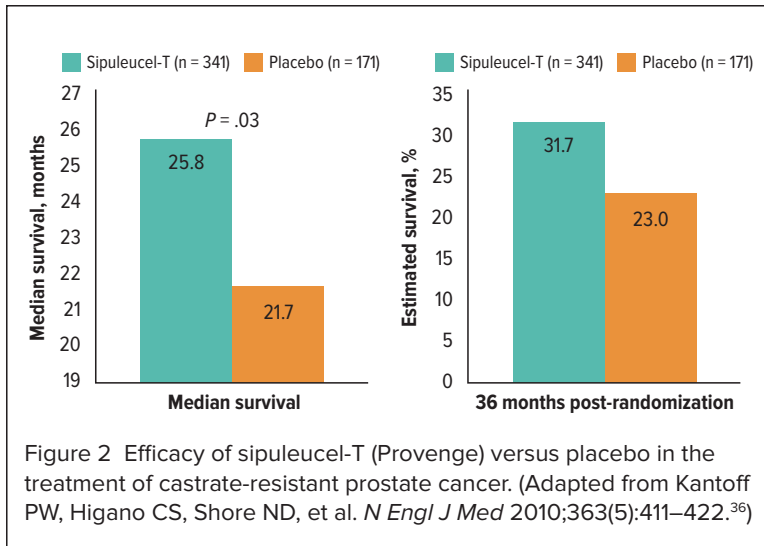
Table 2 Disease Progression With Cabazitaxel (Jevtana) and Mitoxantrone (Novantrone)

Progression Endpoint	Treatment Group		Hazard Ratio (95% CI)	P Value
	Cabazitaxel	Mitoxantrone		
Median time to tumor progression, months	8.8	5.4	0.61 (0.49–0.76)	<0.0001
Median time to PSA progression, months	6.4	3.1	0.75 (0.63–0.90)	0.001
Median time to pain progression, months	Not reached	11.1	0.91 (0.69–1.19)	0.52

CI = confidence interval; PSA = prostate-specific antigen.

Adapted from de Bono JS, Oudard S, Ozguroglu M, et al. *Lancet* 2010;376(9747):1147–1154.³³

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for patients experiencing gastrointestinal toxicities include rehydration, antiemetic medications, and antidiarrheal agents, as well as adherence to current guidelines for administration of prophylactic white blood cell growth factor.^{7,32} In addition, treatment delays or dose reductions to 20 mg/m² may be required for patients experiencing grade 3 or higher diarrhea.³²

Cabazitaxel received FDA approval in 2010 for the treatment of men with metastatic CRPC who previously had been treated with a docetaxel-based regimen.³² The medication is discussed in this month's Drug Forecast article on page 440.

Sipuleucel-T (Provenge)

Sipuleucel-T is an autologous active cellular immunotherapy consisting of peripheral blood mononuclear cells, including antigen-presenting cells (APCs), that have been activated with prostatic acid phosphatase (PAP) and granulocyte-macrophage colony-stimulating factor (GM-CSF), a recombinant human

protein.³⁴ Although the precise mechanism of action is not yet understood,³⁴ it is hypothesized that the activated APCs promote endogenous T cells to destroy PAP-bearing prostate cancer cells.³⁵ Sipuleucel-T is the first in a new class of cancer immunotherapeutic agents to be approved by the FDA (in 2010) for the treatment of asymptomatic or minimally symptomatic metastatic CRPC.^{20,34,35}

A phase 3, multicenter, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of sipuleucel-T compared with placebo.³⁶ Eligible study participants included men with minimally symptomatic or asymptomatic metastatic CRPC who were expected to live at least 6 months. Patients were randomly assigned, in a 2:1 ratio, to receive sipuleucel-T (n = 341) or placebo (n = 171). Treatment was administered every 2 weeks for three cycles. The primary endpoint was overall survival, and the time to objective disease progression was a secondary endpoint.³⁶

At the median follow-up of 34.1 months, a 22% reduction in mortality risk was evident for patients receiving sipuleucel-T (adjusted HR, 0.78; 95% CI, 0.61–0.98; *P* = 0.02). Median survival time and the estimated probability of survival 36 months following randomization are shown in Figure 2, which illustrates the superiority of sipuleucel-T compared with placebo.³⁶ The most common adverse events affecting patients in the two treatment arms are summarized in Table 3.³⁶

An earlier phase 3 trial enrolled 127 patients with asymptomatic CRPC and failed to achieve the primary endpoint of time to disease progression, with a median time to progression of 11.7 weeks (95% CI, 9.1–16.6) for sipuleucel-T and 10.0 weeks (HR, 1.45; 95% CI, 8.7–13.3; 95% CI, 0.99–2.11 for placebo; *P* = 0.52).³⁷ However, sipuleucel-T demonstrated a statistically significant survival advantage at the 36-month follow-up, with a median overall survival of 25.9 months (95% CI, 20.0–31.9) compared with 21.4 months (95% CI, 12.3–25.8) for the placebo group (HR, 1.70; 95% CI, 1.13–2.56; *P* = 0.01). In addition, estimated survival rates were 34% for those in the sipuleucel-T arm compared with 11% for those treated with placebo (*P* = 0.005) at the last assessment prior to censoring at the 36-month follow-up.³⁷

Sipuleucel-T is recommended for patients with good performance status (i.e., a score of 0–1, according to Eastern Cooperative Oncology Group [ECOG] criteria), an estimated life expectancy of at least 6 months, no evidence of visceral disease, and no (or minimal) symptoms.^{7,34} Currently, sipuleucel-T is not considered an appropriate therapy for rapidly progressive prostate cancer.⁷

Abiraterone Acetate (Zytiga)

Abiraterone acetate is a selective inhibitor of cytochrome P450 C17 (CYP17), an

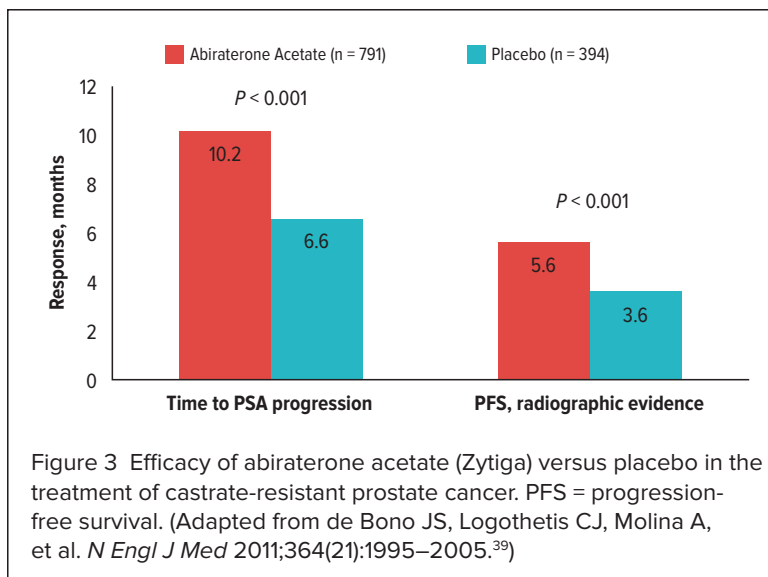
Table 3 Most Frequent Adverse Events in 20% or More Patients Receiving Sipuleucel-T (Provenge) or Placebo

Adverse Event	Sipuleucel-T (n = 338)		Placebo (n = 168)	
	No. (%)	No. (%)	No. (%)	No. (%)
	All Grades	Grade 3–5	All Grades	Grades 3–5
Any	334 (98.8)	107 (31.7)	162 (96.4)	59 (35.1)
Chills	183 (54.1)	4 (1.2)	21 (12.5)	0 (0.0)
Fatigue	132 (39.1)	4 (1.2)	21 (12.5)	3 (1.8)
Back pain	116 (34.3)	12 (3.6)	61 (36.3)	8 (4.8)
Pyrexia	99 (29.3)	1 (0.3)	23 (13.7)	3 (1.8)
Nausea	95 (28.1)	2 (0.6)	35 (20.8)	0 (0.0)
Arthralgia	70 (20.7)	7 (2.1)	40 (23.8)	5 (3.0)
Citrate toxicity*	68 (20.1)	0 (0.0)	34 (20.2)	0 (0.0)

*Citrate toxicity is associated with leukapheresis. Paresthesia and oral paresthesia are considered to be likely symptoms of citrate toxicity.

Adapted from Kantoff PW, Higano CS, Shore ND, et al. *N Engl J Med* 2010;363(5):411–422.³⁶

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docetaxel-based regimen and who had evidence of disease progression.³⁴ The primary study endpoint was overall survival from randomization to death from any cause. Prespecified secondary endpoints included PSA response rate, time to PSA progression, and radiographically confirmed progression-free survival. A total of 1,195 patients were assigned, in a 2:1 ratio, to receive either abiraterone (n = 797) or placebo (n = 398).³⁹

The preplanned interim analysis revealed a 35.4% decrease in mortality rates for abiraterone compared with placebo (HR, 0.65; 95% CI, 0.54–0.77; $P < 0.001$). Significant improvements for patients in the abiraterone arm were also reported for time to radiographic progression and PSA progression (Figure 3).³⁹ The HR for time to PSA progression was 0.58 (95% CI, 0.46–0.73; $P < 0.01$), and the HR for radiographically confirmed progression-free survival was 0.67 (95% CI, 0.59–0.78; $P < 0.001$).

enzyme required for the production of testosterone in the testis, adrenal glands, and prostate.^{20,21,38} It offers the convenience of oral administration. Results from phase 1 and 2 trials suggested that it was efficacious for the treatment of chemotherapy-naïve patients with CRPC as well as those who had previously received a docetaxel-based regimen.^{20,21}

A phase 3, randomized, international, double-blind, placebo-controlled trial compared abiraterone 1 g once daily plus prednisone 5 mg twice daily with placebo plus prednisone 5 mg twice daily.³⁹ Eligible participants included men with confirmed metastatic CRPC who had previously received a

The PSA response rate for the abiraterone-treated patients was 29.0%, compared with 6.0% for the placebo group ($P < 0.001$). Adverse events affecting 20% or more of patients enrolled in the trial are presented in Table 4.³⁹ The results of the interim analysis led to a recommendation by the data monitoring committee to unblind the study and to the FDA's approval of abiraterone plus prednisone for the treatment of metastatic CRPC following therapy with a docetaxel-based regimen.^{21,38}

The COU-AA-302 Trial

COU-AA-302, an international, randomized, double-blind, phase 3 trial, was undertaken to compare abiraterone acetate 1,000 mg plus prednisone 5 mg twice daily with placebo.⁴⁰ A total of 1,088 patients with metastatic CRPC who had not previously been treated with chemotherapy were assigned to one of the two study groups.

Co-primary endpoints included radiographic progression-free survival and overall survival. Results from a planned interim analysis revealed a statistically significant improvement in both primary endpoints for abiraterone as well as median time to opiate use, time to chemotherapy initiation, time to deterioration in ECOG performance status scores, and time to PSA progression.⁴⁰

Notably, median time to radiographic progression-free survival was not reached for the abiraterone arm, compared with 8.3 months for the placebo group (HR, 0.43; 95% CI, 0.35–0.52; $P < 0.0001$), and median overall survival was not reached for patients receiving abiraterone (27.2 months for placebo) (HR, 0.75; 95% CI, 0.61–0.93; $P = 0.0097$).⁴⁰

Abiraterone was approved in April

Table 4 Most Frequent Adverse Events Affecting 20% or More Patients Receiving Abiraterone Acetate (Zytiga) or Placebo

Adverse Event	Abiraterone Acetate (n = 791)		Placebo (n = 394)	
	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4
Anemia	178 (22.5)	59 (7.5)	104 (26.4)	29 (7.4)
Thrombocytopenia	28 (3.5)	11 (1.4)	13 (3.3)	2 (0.5)
Diarrhea	139 (17.6)	5 (0.6)	53 (13.5)	5 (1.3)
Fatigue	346 (43.7)	66 (8.3)	169 (42.9)	39 (9.9)
Asthenia	104 (13.1)	18 (2.3)	52 (13.2)	8 (2.0)
Back pain	233 (29.5)	47 (5.9)	129 (32.7)	38 (9.6)
Nausea	233 (29.5)	13 (1.6)	124 (3.1)	10 (2.5)
Vomiting	168 (21.2)	14 (1.8)	97 (24.6)	11 (2.8)
Constipation	206 (26.0)	8 (1.0)	120 (30.5)	4 (1.0)
Arthralgia	215 (27.2)	33 (4.2)	89 (22.6)	16 (4.1)
Bone pain	194 (24.5)	44 (5.6)	110 (27.9)	29 (7.4)
Fluid retention and edema	241 (30.5)	18 (2.3)	77 (19.5)	4 (1.0)

Adapted from de Bono JS, Logothetis CJ, Molina A, et al. *N Engl J Med* 2011;364(21):1995–2005.³⁹

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2011 in combination with prednisone for the treatment of patients with CRPC who had received prior chemotherapy with docetaxel. At the time of this publication, abiraterone was under review for approval by the FDA for the treatment of chemotherapy-naïve patients with CRPC.

THERAPIES FOR BONE METASTASES

Zoledronic Acid (Zometa)

Metastatic prostate cancer frequently affects the bone and is associated with significant skeletal-related events (SREs), characterized by pathological fractures and spinal cord compression often necessitating radiation or surgery to provide pain relief. Until recently, the bisphosphonate zoledronic acid (Zometa, Novartis) was the mainstay of treatment for patients with bone metastases associated with CRPC.

A randomized, placebo-controlled, phase 3 trial was designed to compare the efficacy and safety of zoledronic acid at dosages of 4 mg and 8 mg with placebo administered once every 3 weeks. The study protocol was subsequently amended to reduce the dose of zoledronic acid to 4 mg because of renal toxicity associated with the 8-mg dose. All patients also received supplemental calcium 500 mg and vitamin D 400 to 500 IU daily. SREs occurred in 44% of patients receiving placebo and in 33.2% of those receiving zoledronic acid 4 mg, for a difference of -11.0% (95% CI, -20.3 to -1.8; $P = 0.21$).⁴¹

Importantly, zoledronic acid is excreted primarily via the renal system, and the risk of renal toxicities is increased for patients with impaired renal function. Zoledronic acid is contraindicated for patients with severe renal dysfunction, such as a baseline creatinine clearance (CrCl) below 30 mL/minute. Dose reductions are required for patients with baseline CrCl levels below 60 mL/minute.⁴²

Denosumab (Xgeva)

Denosumab (Xgeva, Amgen) is a human monoclonal antibody that binds to the human receptor activator of nuclear factor kappa-B ligand (RANKL), a protein that contributes to the formation, function, and survival of osteoclasts. Denosumab inhibits the RANKL on the surface of osteoclasts, thereby preventing bone destruction.^{20,21,43} Denosumab has been approved for the prevention of SRE in patients with bone metastases caused by solid tumors, including prostate cancer.⁴³

A randomized, multicenter, international, blinded, double dummy phase 3 trial compared denosumab with zoledronic acid.⁴⁴ All patients had current or prior radiographic evidence of at least one bone metastasis and failure to respond to at least one prior hormonal therapy. A total of 1,904 patients were assigned, in a 1:1 ratio, to the two treatment groups: 950 received denosumab 120 mg plus intravenous placebo, and 951 received zoledronic acid 4 mg plus subcutaneous placebo, administered every 4 weeks. Dose adjustments for zoledronic acid, as recommended in the prescribing information, were made at baseline according to the Cockcroft–Gault formula for CrCl values.⁴⁴

The median time to the first SREs in the denosumab group was 20.7 months (95% CI, 18.8–24.9) compared with 17.1 months for the zoledronic acid group (95% CI, 15.0–19.4). This reflected an 18% reduction in the time to the first SRE among patients treated with denosumab (HR, 0.82; 95% CI, 0.71–0.95; $P = 0.0002$

for non-inferiority and $P = 0.0008$ for superiority). A significant delay between the time of first and subsequent SREs was also evident for denosumab, compared with zoledronic acid, with a total of 494 SREs reported for denosumab and 584 SREs reported for zoledronic acid (rate ratio, 0.82; 95% CI, 0.71–0.94; adjusted $P = 0.008$).⁴⁴

Overall rates of adverse events, serious adverse events, and fatal adverse events were comparable between the two treatment groups, although the rate of grade 3 or 4 adverse events was significantly higher for those in the denosumab arm (72%) compared with those in the zoledronic acid arm (66%) ($P = 0.01$). Of the patients who received denosumab, 13% experienced hypocalcemia, compared with 6% of those who received zoledronic acid ($P < 0.0001$).⁴⁴

EMERGING THERAPIES IN PHASE 3 TRIALS

In addition to the four new treatment options for CRPC described earlier, several agents are in phase 3 trials, and preliminary results suggest that treatment options for CRPC will continue to expand in the near future. Two novel hormonal therapies—MDV3100 (enzalutamide, Medivation/Astellas) and TAK-700 (orteronel, Millennium Takeda Oncology)—target the androgen receptor pathway.^{20,21}

Phase 3 trials are also under way for two immunotherapeutic agents: ipilimumab (Yervoy, Bristol-Myers Squibb), which was approved in 2011 for the treatment of melanoma, and ProstateVax (Bavarian Nordic), a vaccine. Radium-223 chloride (Alpharadin, Algeta/Bayer) is under evaluation in a phase 3 trial for patients with symptomatic CRPC and bone metastases.^{18,19}

Hormonal Therapies

MDV3100 (Enzalutamide)

MDV3100 is an oral, second-generation, selective androgen receptor antagonist with favorable preclinical and early phase clinical trial results for the treatment of metastatic CRPC. Two phase 3 trials are ongoing: PREVAIL (Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naïve Patients With Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy) and AFFIRM (Safety and Efficacy Study of MDV3100 in Patients With Castration-Resistant Prostate Cancer Who Have Been Previously Treated With Docetaxel-Based Chemotherapy).

The PREVAIL Trial. Results are pending from PREVAIL. This study is being conducted to evaluate MDV3100 in men with CRPC who have not been previously treated with chemotherapy.⁴⁵

The AFFIRM trial. In this randomized, double-blind, placebo-controlled, international study, 1,199 patients were assigned, in a 2:1 ratio, to receive MDV3100 160 mg/day or placebo. The planned interim analysis, at 520 deaths, revealed a 37% reduction in mortality risk with MDV3100 compared with placebo (HR, 0.631; $P < 0.0001$).^{46,47} Figure 4 illustrates the estimated median survival times for both groups, revealing a median difference in overall survival of 4.8 months.^{46,47}

Progression-free survival, based on radiographic results, was 60% longer for the MDV3100 group at 8.3 months, compared with 2.9 months for the placebo group (HR = 0.404; 95% CI, 0.350–0.466; $P < 0.0001$). Median time to PSA progression was 8.3 and 3.0 months for MDV3100 and placebo, respectively

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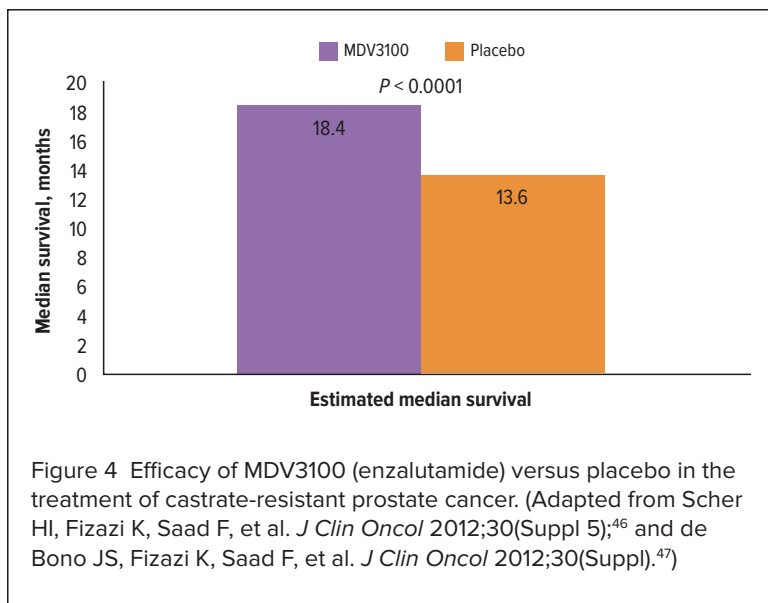


Figure 4 Efficacy of MDV3100 (enzalutamide) versus placebo in the treatment of castrate-resistant prostate cancer. (Adapted from Scher HI, Fizazi K, Saad F, et al. *J Clin Oncol* 2012;30(Suppl 5);⁴⁶ and de Bono JS, Fizazi K, Saad F, et al. *J Clin Oncol* 2012;30(Suppl).⁴⁷)

TAK-700 (Orteronel)

TAK-700, an oral inhibitor of CYP17, has demonstrated reductions in serum PSA levels and partial tumor responses in a phase 1/2 trial of 96 men with metastatic CRPC.⁴⁸ Based on these favorable responses, Millennium is recruiting participants for two multinational randomized, double-blind phase 3 studies—ELM-PC (Evaluation of the Lyase inhibitor in Metastatic Prostate Cancer).⁴⁹

The C21004 Trial. C21004 is designed to compare TAK-700 with placebo for chemotherapy-naïve patients with metastatic CRPC. This randomized, double-blind, multicenter trial is expected to recruit 1,454 study participants. Primary endpoints are radiographic progression-free survival and overall survival. Secondary endpoints are PSA response at 12 weeks, changes in circulating tumor cell counts, and time to pain progression.⁵⁰

The C21005 Trial. TAK-700 is combined with prednisolone or placebo to treat men with metastatic CRPC that has progressed despite previous docetaxel-based therapy.^{50,51} Approximately 1,083

men will be recruited. The primary endpoint is overall survival; secondary endpoints are PSA response and pain response at 12 weeks as well as radiographic progression-free survival from randomization to disease progression or death.⁵¹

Immunotherapies

Ipilimumab (Yervoy)

Ipilimumab is a human anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) monoclonal antibody that inhibits activation of CTLA-4, which promotes a T-cell-mediated immune response.^{20,21} Results from a phase 2 trial demonstrated greater reductions in serum PSA levels at 3 months for patients with advanced prostate cancer who were treated with ADT plus ipilimumab (55%) compared with those who received ADT alone (38%).⁵²

Two randomized, double-blind, multicenter, phase 3 trials are currently under way to further evaluate the role of ipilimumab for the treatment of advanced CRPC. The first trial expects to enroll an estimated 800 patients with CRPC and at least one bone metastasis following progression after docetaxel therapy to compare ipilimumab with placebo following radiation therapy. The primary study endpoint is overall survival, and secondary endpoints include progression-free survival, pain response, and safety.⁵³

The second randomized, double-blind, phase 3 trial is being conducted to evaluate the efficacy and safety of ipilimumab compared with placebo in asymptomatic or minimally symptomatic patients with metastatic CRPC who have not received prior chemotherapy.⁵⁴ Overall survival has been established as the primary study endpoint. Progression-free survival, pain response, and safety are included as secondary endpoints.

Approximately 600 patients are expected to be enrolled and observed from randomization to date of death.⁵⁴

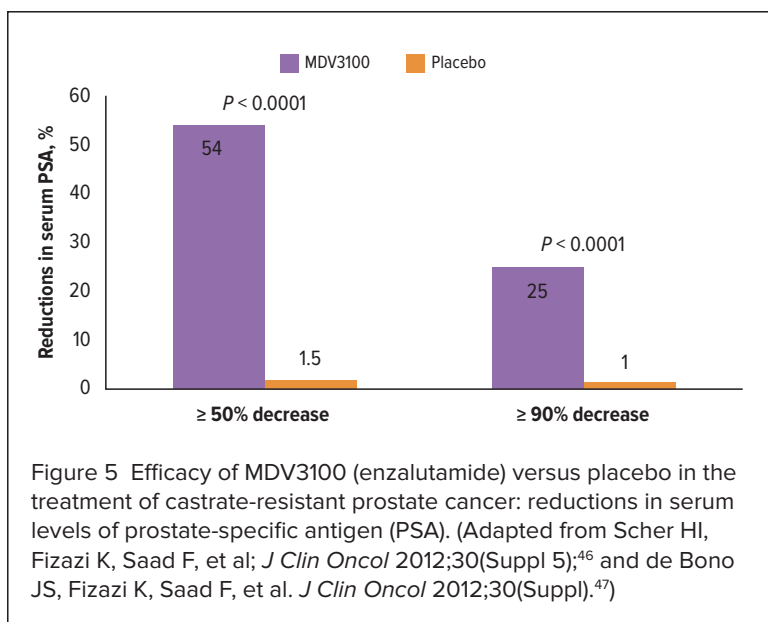


Figure 5 Efficacy of MDV3100 (enzalutamide) versus placebo in the treatment of castrate-resistant prostate cancer: reductions in serum levels of prostate-specific antigen (PSA). (Adapted from Scher HI, Fizazi K, Saad F, et al; *J Clin Oncol* 2012;30(Suppl 5);⁴⁶ and de Bono JS, Fizazi K, Saad F, et al. *J Clin Oncol* 2012;30(Suppl).⁴⁷)

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ProstVac

ProstVac is a novel cancer vaccine consisting of fowlpox and vaccinia PSA vaccines administered in combination with three co-stimulatory molecules, including intracellular adhesion molecule-1, B7, and leukocyte function-associated antigen.^{20,55} A phase 2 trial was conducted with 122 patients who had mildly symptomatic metastatic CRPC. These patients were randomly assigned to receive either ProstVac (n = 82) with GM-CSF or a control vaccine (n = 40). Although progression-free survival did not differ significantly between the two treatment arms ($P = 0.60$), patients receiving ProstVac demonstrated better overall survival; 30% were still living at the 3-year follow-up compared with 17% of the control group. In addition, median survival was 8.5 months longer with ProstVac than with the control vaccine (25.1 vs. 16.6 months, respectively; HR = 0.56; 95% CI, 0.37–0.85; log-rank $P = 0.0061$).⁵⁵

These promising results led to the initiation of a randomized, double-blind phase 3 trial of ProstVac alone, ProstVac plus GM-CSF, or placebo for men with asymptomatic or minimally symptomatic metastatic CRPC. A total of 1,200 patients will be recruited for trial enrollment with overall survival the primary study endpoint. A secondary endpoint is the proportion of patients in each of the two ProstVac groups who do not experience radiological progression of disease, pain progression, initiation of chemotherapy, or death at 6 months compared with placebo.⁵⁶

Bone-Targeting Agents

Radium-223 (Alpharadin)

Results from a phase 2 trial of radium-223, a bone-seeking radionuclide, offer a promising treatment alternative for bone metastases associated with CRPC.⁵⁷ Patients received four injections of radium-223 (n = 33) or placebo (n = 31) on 4-week cycles. The primary endpoints were changes in bone-alkaline phosphatase concentrations and time to SREs. Secondary endpoints focused on safety, serum markers of bone turnover, time to PSA progression, and overall survival.⁵⁷

The median relative change in bone-alkaline phosphatase levels, from baseline to 4 weeks following the last study injection, was -65.6% (95% CI, -69.5 to -57.7) for the radium-223 group compared with 9.3% (95% CI, 3.8–60.9) for controls ($P < 0.0001$). The adjusted HR for time to the first SRE was 1.75 (95% CI, 0.96–3.19; $P = 0.065$).

The median times to the first SRE were 14 weeks for the radium-223 group (95% CI, 9–30) and 11 weeks for the control group (95% CI, 5–25).

The median times to PSA progression were 26 weeks for the radium-223 group (95% CI, 16–39) and 8 weeks for the control group (95% CI, 4–12) ($P = 0.048$). The adjusted HR for overall survival was 2.12 (95% CI, 1.13–3.98; $P = 0.020$). Median overall survival was 65.3 weeks for patients treated with radium-223 compared with 46.4 weeks for those in the control arm (log-rank $P = 0.66$).⁵⁷

The ALSYMPCA Trial. Alpharadin in SYMptomatic Prostate CAncer, a phase 3, double-blind, randomized, international trial, is being conducted to compare radium-223 plus best standard of care with placebo and best standard of care for patients with bone metastases associated with CRPC.

In a 2:1 ratio, patients receive six injections of radium-223 (50 kilobecquerels ([kBq/kg]) or placebo every 4 weeks. A total of 921 patients were included (614 receiving radium-223 and 307 receiving placebo).⁵⁸

Significant improvements were reported for overall survival in the radium-223 arm at 14.9 months compared with 11.3 months for the placebo arm (HR, 0.695; 95% CI, 0.581–0.832; $P = 0.00007$). In addition, the time to the first SRE was 15.6 months for radium-223 and 9.8 months for placebo (HR, 0.658; 95% CI, 0.552–0.830; $P = 0.00037$). The safety profile was favorable for radium-223, with 2.2% of patients experiencing grade 3 or 4 myelosuppression compared with 0.7% of those treated with placebo. Rates of grade 3 or 4 thrombocytopenia were 6.3% for the radium-223 group and 2.0% for the placebo arm.⁵⁸

In additional analyses of ALSYMPCA, radium-223 significantly delayed time to the first SRE (13.6 months) compared with placebo (8.4 months) (HR, 0.610; 95% CI, 0.461–0.807; $P = 0.00046$).⁵⁹ Radium-223 has been granted a fast-track approval designation by the FDA for the treatment of bone metastases associated with CRPC.

CONCLUSION

Tremendous strides have been made in the identification of new treatments for CRPC and bone-related metastases. Four new agents, including cabazitaxel, sipuleucel-T, abiraterone acetate, and denosumab received FDA approval for CRPC or SRE since 2010, and five new treatments have demonstrated positive results in phase 3 trials, suggesting that additional therapies may soon be approved for the management of metastatic CRPC. However, research has not yet clarified which patients will achieve optimal benefit from these agents. Specifically, there are no predictive models or biomarkers to identify patients who are likely to benefit from approved and anticipated new regimens, including those that target skeletal complications that are characteristic of metastatic CRPC.^{20,21}

Of particular concern is the determination of the appropriate sequencing for administration of newly approved and emerging therapies.^{19–21} Algorithms for risk stratification and development of nomograms to estimate individual probabilities of survival will play a key role in facilitating physicians' efforts to select the optimal therapy for individual patients.²⁰

Research is also needed to develop and refine the application of biologic and clinical measures of treatment response, including tumor imaging; PSA measures such as doubling time; and biomarkers of angiogenesis, inflammatory cytokines, and bone turnover. These measures should be augmented by assessments of patient quality of life such as pain, the use of medications for pain, and patient-reported quality-of-life measures.²⁰

It is likely that the most favorable clinical and safety outcomes will be achieved from the sequential use of multiple agents. Accomplishing this goal will require multidisciplinary health care teams, including urologists, medical oncologists, and radiation oncologists, to achieve continuity and a continuum of care. Assessment of patient preferences regarding treatment options, as well as regular communication among all members of the care team, will be essential to achieve the best clinical outcomes for all patients.²⁰

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