New Agents in Metastatic Prostate Cancer

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Abstract

Discoveries of molecular mechanisms and therapeutic targets in metastatic castration-resistant prostate cancer (CRPC) have led to significant advancements in the development of effective agents in this setting, with diverse mechanisms of action. Within the past 2 years, 5 agents have been approved for the treatment of patients with metastatic CRPC (cabazitaxel, abiraterone, sipuleucel-T, denosumab, and enzalutamide), and another (Alpharadin) has shown overall survival benefit in a phase III trial. This article summarizes the phase III data showing clinical benefit from these agents, highlights other promising therapies in phase III studies as single agents (PROSTVAC-VF, ipilimumab, cabozantinib), discusses important unanswered questions regarding these therapies, and provides a schema for their use based on current regulatory approval and how this is likely to evolve as data from ongoing studies are reported. Although curative interventions in metastatic CRPC still do not exist, the hope is that optimization of therapeutic strategies can reduce the morbidity and mortality associated with this disease. (*JNCCN* 2012;10:1403–1409)

Taxanes

Until recently, no agents had shown improved overall survival compared with placebo in patients with metastatic castration-resistant prostate cancer (CRPC) whose disease progressed after docetaxel treatment. However, recent phase III studies have dramatically altered the landscape in this population (Table 1). Cabazitaxel is a novel taxane with activity in preclinical models of cancer resistant to paclitaxel and docetaxel[1,2] and was compared with mitoxantrone in the post-docetaxel setting by the TROPIC investigators.[3] In this phase III study, patients received 10 mg of prednisone daily and were randomized to receive either 12 mg/m^2 of mitoxantrone or 25 mg/m^2 of cabazitaxel intravenously every 3 weeks. The primary end point was met, with improved overall survival of 15.1 months (95% CI, 14.1–16.3) in the cabazitaxel group compared with 12.7 months (95% CI, 11.6–13.7) in the mitoxantrone group (hazard ratio [HR], 0.70; 95% CI, 0.59–0.83; *P*<.0001), accompanied by improvements in response rates (14.4% vs. 4.4%; *P*=.0005) and progression-free survival (2.8 vs. 1.4 months, *P*<.0001). This agent has been approved by the FDA in the post-docetaxel setting because of this observed clinical activity.

However, cabazitaxel was accompanied by increased toxicity compared with mitoxantrone, with higher rates of grade 3 or greater neutropenia (82% vs. 58%), neutropenic fever (8% vs. 1%), and diarrhea (6% vs. <1%), along with greater requirements for dose reductions (12% vs. 4%) and discontinuations of treatment because of adverse events (18% vs. 8%). In addition, more patients died within 30 days of the last dose of the study drug in the cabazitaxel group versus the mitoxantrone group (5% vs. 2%), although the statistical significance of these differences was not reported. Thus, caution should be exercised in the administration of this agent with close monitoring, low thresholds for dose reductions, and consideration of growth factor support with granulocyte colony-stimulating factor in patients at high risk. Remaining questions include whether cabazitaxel is superior to docetaxel in the first-line setting and whether a lower dose of cabazitaxel may have similar clinical activity with lower toxicity compared with the

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Table 1 Comparison, Clinical End Points, and Benefits in Metastatic CRPC Trials

Trial/Agent Approved	Disease State	Comparator	End Point	Median Months Benefit	Hazard Ratio	*P* Value
TAX327[35] docetaxel, 2004	Metastatic CRPC	Mitoxantrone Prednisone	OS	2.5	0.76	.009
IMPACT[17] sipuleucel-T, 2010	Pre- and post-docetaxel CRPC	Placebo	OS	4.1	0.775	.032
TROPIC[3] cabazitaxel, 2010	Post-docetaxel CRPC	Mitoxantrone Prednisone	OS	2.4	0.70	<.0001
COU-AA-301[10] abiraterone, 2011	Post-docetaxel CRPC	Placebo Prednisone	OS	3.9	0.646	<.0001
COU-AA-302[12] abiraterone, 2012	Pre-docetaxel CRPC	Placebo Prednisone	OS	(Median not reached in abiraterone group)	0.75	.0097
AFFIRM[14] MDV3100	Post-docetaxel CRPC	Placebo	OS	4.8	0.63	<.0001
ALSYMPCA[27] alpharadin	Post-docetaxel (or unfit for chemotherapy) CRPC	Placebo	OS	2.8	0.69	.00185
ZA,[36] 2002	CRPC with bone metastases	Placebo	SRE	(Median not reached in ZA group)		.011
Denosumab,[28] 2011	CRPC with bone metastases	ZA	SRE	3.6	0.82	.008

Abbreviations: CRPC, castration-resistant prostate cancer; OS, median overall survival; SRE, median time to skeletal-related event; ZA, zoledronic acid.

dose used in the TROPIC study. These questions are being studied in the FIRSTANA trial (ClinicalTrials.gov identifier: NCT01308567) in which chemotherapy-naïve patients with CRPC are treated with prednisone at 10 mg/d and randomized to docetaxel at 75 mg/m^2, cabazitaxel at 20 mg/m^2, or cabazitaxel at 25 mg/m^2 every 3 weeks, with the primary end point of overall survival.

Hormonal Agents

Many prostate cancers that progress after treatment with castration and first-generation antiandrogens remain dependent on androgen receptor signaling for growth and survival, thus providing a rationale for continued therapeutic targeting of this pathway with secondary hormonal manipulations.[4,5] Among these manipulations is inhibition of the CYP17A1 (17α-hydroxylase/17,20-lyase) enzyme required for both adrenal and intratumoral androgen synthesis[6,7] to further decrease androgen concentrations below castrate levels. A first-generation inhibitor of this enzyme is the antifungal agent ketoconazole, which in combination with hydrocortisone has shown clinical responses in patients with CRPC,[8] although it has not been shown to prolong survival in this population.[9] Abiraterone is a novel and more potent inhibitor of CYP17A1, which has recently been shown to improve overall survival in patients with CRPC who had disease progression after treatment with docetaxel in the COU-AA-301 trial.[10] In this study, patients received 5 mg of prednisone twice daily and were randomized 2:1 to receive abiraterone acetate at 1 g/d orally versus placebo. Overall survival was improved in the abiraterone group (14.8 vs. 10.9 months; HR, 0.65; 95% CI, 0.54–0.77; *P*<.001), as was progression-free survival (5.6 vs. 3.6 months; *P*<.001) and prostate-specific antigen (PSA) response rate (29% vs. 6%; *P*<.001). In prior studies,[11] treatment with abiraterone was accompanied

by signs and symptoms of mineralocorticoid excess (hypertension, fluid retention/edema, hypokalemia) from accumulation of androgen precursors with mineralocorticoid properties, although these were ameliorated with the addition of daily prednisone. The COU-AA-301 study showed increased rates of fluid retention/edema (31% vs. 22% in the placebo group; *P*=.04) and hypokalemia (17% vs. 8% in the placebo group; *P*<.001), primarily grades 1 or 2. A nonsignificant increase in cardiac events was also seen in the abiraterone group (13% vs. 11%; *P*=.14), primarily grade 1 or 2 tachycardia or grade 3 or less atrial fibrillation, with no differences in fatal cardiac events. The study was unblinded at interim analysis because of clinical efficacy, and this agent has been FDA-approved in the post-docetaxel population.

Interim results of a phase III study of abiraterone plus prednisone versus placebo plus prednisone in asymptomatic or mildly symptomatic patients with metastatic CRPC who have not received prior cytotoxic chemotherapy (COU-AA-302; ClinicalTrials.gov identifier: NCT00887198) were reported at the 2012 ASCO Annual Meeting.[12] Interim analysis conducted by the Independent Data Monitoring Committee (IDMC) recommended the trial be unblinded and the active drug be given to patients receiving placebo based on differences in median radiographic progression-free survival (end point not reached [NR] for abiraterone vs. 8.3 months for placebo; *P*<.0001), overall survival (NR vs. 27.2 months; *P*=.0097), and secondary end points as evidence of clinical benefit and continued evidence of favorable safety.

Another novel secondary hormonal agent is the small molecule enzalutamide, also known as MDV3100, a potent inhibitor of androgen receptor signaling that prevents androgen binding to the androgen receptor and androgen receptor translocation into the nucleus.[13] In the phase III AFFIRM study,[14] patients with CRPC who had previously received docetaxel were randomized 2:1 to receive enzalutamide, 160 mg/d versus placebo, and enzalutamide was found to confer significant overall survival benefit (*P*<.001; HR, 0.631), with an estimated median overall survival of 18.4 months in the enzalutamide arm compared with 13.6 months in the placebo arm. Improvements in multiple secondary end points were also seen, including radiographic (8.3 vs. 2.9 months; HR, 0.40; *P*<.001) and PSA (8.3 vs. 3.0 months; HR, 0.25; *P*<.001) progression-free survival. Fewer grade 3 or greater adverse events were seen in the enzalutamide group than in the placebo group (45.3% vs. 53.1%), but higher incidences of all grades of fatigue (34% vs. 29%), diarrhea (21% vs. 18%), hot flashes (20% vs. 10%), musculoskeletal pain (14% vs. 10%), and headache (12% vs. 6%) were seen with enzalutamide (statistical significance for these events was not reported). Also, up to 7 of the 800 patients treated with enzalutamide experienced a seizure (5 reported by the investigators) between 31 and 603 days after initiating treatment, with no seizures in the control group. Therefore, this medication is not recommended for patients with predisposing factors for seizure, such history of seizure, cerebral vascular accident or recent transient ischemic attack, brain metastases, or concomitant use of other medications that may lower the seizure threshold (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203415lbl.pdf).

Enzalutamide was recently FDA-approved for the treatment of patients with metastatic CRPC who have previously received docetaxel; the efficacy of enzalutamide in chemotherapy-naïve patients is currently under study in the PREVAIL trial (ClinicalTrials.gov identifier: NCT01212991).

Immunotherapy

Multiple immune-based therapies hold promise for the treatment of metastatic CRPC,[15,16] and the first immunotherapy to demonstrate an overall survival benefit in this setting is the tumor vaccine sipuleucel-T. This agent is generated by isolating autologous peripheral blood mononuclear cells, including antigen-presenting cells, through leukapheresis and then culturing them for 36 to 44 hours at 37°C with media containing the recombinant fusion protein PA2024, consisting of prostatic acid phosphatase fused to granulocyte-macrophage colony-stimulating factor. The product, containing a minimum of 40 million large cells expressing the costimulatory molecule CD54 per dose, is then infused back into the patients approximately 3 days after leukapheresis.

In the IMPACT study,[17] asymptomatic or minimally symptomatic patients with metastatic CRPC were randomized 2:1 to receive 3 infusions of sipuleucel-T or placebo (antigen-presenting cells cultured in media at 2°C–8°C without PA2024). Patients in

the sipuleucel-T arm had a prolonged overall survival of 25.8 months compared with 21.7 months in the placebo group, and a relative reduction of 22% in the risk of death compared with the placebo group (HR, 0.78; 95% CI, 0.61–0.98; *P*=.03). This benefit was evident even though crossover was allowed in the study, such that 49.1% of patients in the placebo arm received a version of sipuleucel-T prepared from cryopreserved cells (APC8015F) as their first subsequent therapy after progression. Interestingly, no difference in PSA response rate or progression-free survival was associated with this therapy, and Kaplan-Meier survival curves for sipuleucel-T versus placebo only diverge more than 6 months after registration. The mechanisms of overall survival benefit without improving time to progression remain unclear; possible explanations are that effects of sipuleucel-T would only manifest after a period necessary for immune activation (≈4–8 weeks) or that the agent may improve the efficacy of subsequent therapies.[18] The lack of objective responses also complicates the identification of patients who benefited from the therapy in order to discover markers predicting response or resistance.

The most common adverse events in the sipuleucel-T group within 1 day after infusion were chills (in 51.2%; 1.2% with grade ≥3), fever (22.5%), fatigue (16.0%; 1.2% with grade ≥3), nausea (14.2%), and headache (10.7%); other adverse events were similar in the sipuleucel-T and placebo groups. Rates of cerebrovascular events were 2.4% in the sipuleucel-T group and 1.8% in the placebo group (not significant) in this study, and 4.0% vs. 2.9%, respectively, (not significant) when combined with data from 2 prior phase III trials (D9901 and D9902A).[19] Given the safety and efficacy of this agent, it has been approved by the FDA for asymptomatic or minimally symptomatic patients with metastatic CRPC who have received prior chemotherapy or are chemotherapy-naïve. The widespread adoption of this intervention is controversial given perceptions regarding the lack of an immediate clinical benefit and the absence of an improvement in progression-free survival,[20,21] which is not entirely surprising given the likely time frame it takes for this therapy to have a clinical impact, but it has been approved for reimbursement by the Centers for Medicaid and Medicare Services as a "necessary and reasonable treatment" (http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=247&ver=12&NcaName=Autologous+Cellular+Immunotherapy+Treatment+of+Metastatic+Prostate+Cancer).

Another agent currently being studied in a phase III trial (PROSPECT; ClinicalTrials.gov identifier: NCT01322490) is PROSTVAC-VF/TRICOM, a tumor vaccine composed of 2 recombinant viral vectors (a vaccinia-based vector for priming and a fowlpox-vector for subsequent boosting), each encoding transgenes for PSA in addition to 3 immune costimulatory molecules (B7.1, ICAM-1, and LFA-3). This agent has previously demonstrated an overall survival benefit in a randomized phase II setting,[22] also without a progression-free survival benefit. As a recombinant product not requiring autologous cells, this agent may provide some advantages in terms of administration compared to sipuleucel-T if also efficacious. Ipilimumab, a fully human monoclonal antibody targeting CTLA-4, a surface molecule that transduces inhibitory signals in T cells, is now being investigated in 2 randomized placebo-controlled phase III trials for patients with metastatic CRPC, in the prechemotherapy (ClinicalTrials.gov identifier: NCT01057810) and postchemotherapy settings (ClinicalTrials.gov identifier: NCT00861614).

Radiopharmaceuticals and Bone-Directed Agents

Given that recent autopsy series have shown bone involvement in nearly all patients who die of prostate cancer,[23] targeting prostate cancer in the bone microenvironment has evolved as an important avenue of study. One strategy that has improved clinical outcomes in these patients is the use of radiopharmaceutical agents,[24] which preferentially deposit at sites of increased osteoblastic activity and emit localized radiation to disseminated bony metastases. The radioisotopes strontium-89 and samarium-153 are FDA-approved for the treatment of bone pain from skeletal metastases based on phase III data,[25,26] but neither agent has yet been shown to prolong survival in a large randomized study. Data are pending from 2 phase III studies of strontium-89 in combination with chemotherapy being conducted by the Cancer Treatment Support Unit of the National Cancer Institute (NCI-3410, ClinicalTrials.gov identifier: NCT00024167) and Cancer Research UK (TRAPEZE, ISRCTN12808747).

Another radiopharmaceutical, radium-223 (Alpharadin), has shown significant promise in the treatment of prostate cancer metastatic to bone. Unlike strontium-89, which primarily emits beta particles, and samarium-153, which emits both beta and gamma particles, radium-223 primarily emits alpha particles. Alpha particles carry higher energy and travel shorter distances than beta and gamma particles, which would theoretically lead to greater efficacy against adjacent tumor cells, with decreased toxicity to distant normal marrow. In the phase III ALSYMPCA study,[27] patients with CRPC post-docetaxel (or unfit for docetaxel) with 2 or more bone metastases and no visceral metastases were randomized 2:1 to receive 6 injections of 50 kBq/kg of radium-223 or placebo at 4-week intervals. The primary end point of prolonged overall survival was achieved, with a median overall survival of 14.0 months in the radium-223 group and 11.2 months in the placebo group (HR, 0.695; 95% CI, 0.552–0.875; *P*=.00185), along with improvement in time to first skeletal-related event (SRE) to 13.6 months for the redium-223 group versus 8.4 months for placebo (*P*=.00046). Survival benefit was seen in both patients who had previously received docetaxel (HR, 0.755; 95% CI, 0.565–1.009) and those who had not (HR, 0.611; 95% CI, 0.423–0.883). Rates of adverse events were very similar in the radium-223 and placebo groups, with fewer discontinuations from adverse events in the radium-223 arm. The trial was terminated early on recommendation of the IDMC because of improved outcomes in preplanned interim analysis, and this agent has been granted Fast Track designation for approval by the FDA.

In addition to radiopharmaceuticals, inhibitors of bone turnover without known significant antitumor activity have also been shown to lead to improvements in clinical outcomes. Denosumab, a fully human monoclonal antibody targeting receptor activator of nuclear factor-κB ligand (RANKL) that inhibits osteoclast-mediated bone destruction, has shown improved time to a composite end point of SREs compared with zoledronic acid in patients with metastatic CRPC[28]: 20.7 months for denosumab (120 mg subcutaneously + intravenous placebo) versus 17.1 months for zoledronic acid (4 mg intravenously every 4 weeks + subcutaneous placebo; *P*=.0002 for noninferiority, *P*=.008 for superiority). However, the rates of pathologic fracture were nearly identical in the 2 arms (14.4% vs. 15.0%) and no difference was seen in overall survival. An increased risk of hypocalcemia was seen in the denosumab arm (13% vs. 6%; *P*<.0001), with a low rate but a trend toward increased osteonecrosis of the jaw (2% vs. 1%; *P*=.09). Denosumab is the preferred treatment to decrease SREs in patients with CRPC with relative contraindications to zoledronic acid, such as renal dysfunction, but given its increased cost and modest benefits compared with zoledronic acid, both agents are reasonable options based on the current data.

Denosumab treatment has recently been reported to increase time to first clinically evident bone metastasis in patients with nonmetastatic CRPC with high-risk features (PSA ≥8.0 µg/L or PSA doubling time ≤10.0 months, or both), from 29.5 months with placebo to 33.2 months with denosumab.[29] However, an increased risk of osteonecrosis of the jaw (5% vs. 0%) and hypocalcemia (2% vs. <1%) was seen in the denosumab arm, and no improvement in overall survival. Although the biology is intriguing, given the cost and potential toxicity of the treatment and unclear clinical benefit of prolonging time to first bone metastasis, denosumab is not FDA-approved for this purpose.

A novel multikinase inhibitor, cabozantinib (XL184), has recently been reported to lead to significant improvements in bony disease in patients with CRPC, with 86% of patients with metastases evaluable by bone scan in a randomized phase II study showing complete or partial resolution of lesions at week 6, accompanied by significant improvements in pain.[30] However, significant toxicity was associated with this drug, with 51% of patients requiring dose reductions and 10% of discontinuations related to adverse events (primarily fatigue, hypertension, and hand-foot syndrome). This agent is currently being compared with mitoxantrone plus prednisone in terms of pain response and bone scan response in patients with previously treated symptomatic CRPC in a phase III trial (COMET-2; ClinicalTrials.gov identifier: NCT01522443). Although cabozantinib is reported to primarily target MET and vascular endothelial growth factor receptor 2 (VEGFR-2), it can also inhibit many other receptor tyrosine kinases (including RET, KIT, FLT3, and TIE2),[31] and therefore the relevant target substrates for its clinical activity remain unclear. As specific pathways

required for prostate cancer survival and growth in the bone microenvironment are clarified, the hope is that more targeted treatments can lead to increased efficacy and decreased toxicity in this context.

Schema

The optimal sequencing of novel agents in prostate cancer, the efficacy of combinations thereof, proper patient selection, and the utility of applying newly approved treatment earlier in the disease course remain unresolved,[32–34] and these issues will continue to increase in complexity as more agents are approved. Treatment with zoledronic acid or denosumab is indicated to reduce SREs in all patients with CRPC metastatic to bone who do not have contraindications to therapy. Based on the current understanding of immunotherapy, sipuleucel-T can be considered first-line therapy for patients with symptomatic or minimally symptomatic metastatic CRPC. For patients with symptomatic metastases, docetaxel remains the first line of therapy pending the results of ongoing phase III studies and regulatory approvals. For patients whose disease progresses after docetaxel therapy, cabazitaxel, abiraterone, and enzalutamide are approved interventions, whereas radium-223 is likely to be approved later this year. Given the relative clinical benefits and toxicities, it is reasonable to reserve the use of cabazitaxel to patients with good performance status whose disease has progressed after treatment with less-toxic therapies. If abiraterone and radium-223 are approved in the prechemotherapy setting, and if enzalutamide shows benefit in the prechemotherapy setting and is approved, docetaxel may likewise be reserved for patients whose disease has progressed after these therapies. Given continued uncertainty regarding the optimal therapeutic strategies incorporating these agents, continued accrual of patients to clinical trials to address these questions remains imperative.

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