Clinical Development of Novel Therapeutics for Castration-Resistant Prostate Cancer

Historic Challenges and Recent Successes

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There have been more drugs approved by the US Food and Drug Administration for the treatment of castration-resistant prostate cancer in the past 3 years than in the prior 3 decades, with additional drugs on the verge of approval based on the results of recently reported randomized trials. While an improvement in the understanding of the pathogenesis of castration-resistant prostate cancer has undeniably accelerated the transition of novel approaches from "bench to bedside," the recent successes in the treatment of prostate cancer are also a result of the efforts of clinical investigators to redefine the framework in which drugs for castration-resistant disease are evaluated. This review will explore the shifting paradigm in drug development for castration-resistant prostate cancer over the past several decades, and highlight how new definitions, trial designs, and endpoints have facilitated the emergence of new therapies for this challenging disease. CA Cancer J Clin 2012;62:299-308. © 2012 American Cancer Society.

Introduction

Clinical drug development for the treatment of castration-resistant prostate cancer (CRPC) has entered a renaissance era. There have been more drugs approved by the US Food and Drug Administration (FDA) for the treatment of CRPC in the past 3 years than in the prior 3 decades, with additional drugs on the verge of approval based on the results of recently reported randomized trials (Fig. 1). An improvement in the understanding of the pathogenesis of CRPC has been central to these recent advances (Fig. 2). However, the effective translation of these laboratory discoveries could not have occurred without the efforts of clinical investigators focused on establishing rational and novel approaches to clinical drug development.

Historical Barriers and Solutions in Drug Development for CRPC

Recognizing the Importance of Symptomatic Improvement

The development of systemic therapy in CRPC has historically been hampered by the difficulty in applying the standard phase 2 measures of response that are used in other solid tumors. The majority of men with metastatic prostate cancer lack measurable sites of disease. While bone metastases are common, evaluating disease response in bone with serial bone scans is problematic. Bone scans are not specific for metastatic deposits, early changes may reflect bone healing rather than bone destruction, and improvements in bone scans often significantly lag behind other clinical indicators of benefit. These challenges in response assessment were at least in part responsible for the historic notion that CRPC was a treatment-resistant disease. In a classic review by Yagoda and Petrylak published in 1993, 26 trials of various systemic treatments (mostly single-agent cytotoxics) for CRPC were reviewed and revealed an aggregated response rate of 8.7% (95% confidence interval [CI], 6.4%-9.0%).1 Response assessments in these trials were extremely heterogeneous and included changes in laboratory, clinical, and imaging parameters.

An appreciation that treatment may be yielding beneficial effects in patients with CRPC beyond what could be measured by conventional imaging led to the design of clinical trials that integrated outcomes focused on symptomatic improvements. In a phase 2 trial of mitoxantrone plus prednisone in patients with CRPC, response was assessed using data from a quality-of-life

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instrument, analgesic intake reports, and pain scores. While only one of the 25 patients studied had a measurable response to treatment, 9 of 25 patients (36%) achieved a palliative response according to the protocol-specific criteria. This led to the design of 2 phase 3 trials evaluating treatment with mitoxantrone plus steroids versus steroids alone, with both trials including quality-of-life assessments, and one trial using pain control as a primary endpoint. Both of these trials demonstrated an improvement in palliation with mitoxantrone therapy, although neither demonstrated a survival benefit. Based on these results, mitoxantrone was approved by the FDA for the treatment of prostate cancer in 1996.

The Introduction of PSA as an Intermediate Endpoint

Because prostate-specific antigen (PSA) is elevated in the majority of patients with advanced prostate cancer, and anecdotal evidence suggested that changes in PSA often antedated changes on bone scan, several groups proposed the use of posttreatment changes in PSA to rapidly screen the activity of novel agents for the treatment of advanced prostate cancer in clinical trials. Retrospective studies subsequently correlated various degrees of posttreatment PSA declines with improved survival in patients with advanced prostate cancer. The first trial of a novel treatment for patients with CRPC to integrate posttreatment changes in PSA was reported by Ferro et al in 1989 and several others followed shortly thereafter. However, many of these trials reported different posttreatment PSA parameters, thereby limiting cross-trial comparisons and ultimately creating confusion with regard to the prioritization of agents for further development.

In an attempt to standardize phase 2 trials of novel therapies in CRPC, a panel of experts formed the Prostate-Specific Antigen Working Group. The group convened at a conference in March 1999 and formulated a series of recommendations for trial design in an attempt to allow clinical investigators developing novel regimens to “speak the same language.” While the group acknowledged that posttreatment decline in PSA had not met the criteria for a true surrogate endpoint, changes in PSA were still considered a valuable aid in screening agents for sufficient activity to warrant moving forward to phase 3 testing. The important recommendations by this group set the stage for the development of a new generation of clinical trials in advanced prostate cancer.

The use of PSA as an intermediate endpoint helped identify agents targeting the microtubules as being particularly active in advanced prostate cancer (initially the vinca alkaloids and subsequently the taxanes). A series of phase 2 trials explored paclitaxel or docetaxel with or without estramustine phosphate. These trials reported posttreatment declines in PSA of $\geq 50\%$ in approximately 50% to 75% of patients, higher rates of objective responses in measurable disease than encountered with previously explored cytotoxics, and frequent palliation of symptoms. Two phase 3 studies were initiated in the late 1990s designed to compare docetaxel-based regimens with mitoxantrone plus prednisone: Southwest Oncology Group
Both of these trials demonstrated an improvement in survival with the docetaxel-based regimens. Based on the results of these studies, the FDA approved the use of docetaxel together with prednisone as first-line therapy for CRPC in May 2004, making it the first drug approved in this setting based on a survival advantage.

Moving Beyond PSA Alone
While the use of PSA as an intermediate endpoint undoubtedly accelerated the development of docetaxel for the treatment of CRPC, subsequent analyses revealed that posttreatment declines in PSA only accounted for a small degree of the variation noted in the outcomes of patients with CRPC and failed to definitively fulfill the Prentice criteria as a true surrogate endpoint. Furthermore, clinical studies suggested that overreliance on PSA alone may compromise the development of novel therapies for CRPC, particularly those with a noncytotoxic mechanism of action. In fact, a disconnect between posttreatment changes in PSA and imaging or symptom parameters emerged in several trials, particularly those exploring antiangiogenic therapy. In a trial of sunitinib in patients with CRPC, several men achieved stable or improved disease on cross-sectional imaging and/or bone scan, but demonstrated continued rises in their serum PSA values. Insight into the importance of mechanism of action in the selection of appropriate study endpoints in CRPC was perhaps first highlighted by the development strategy for the bisphosphonates. Because progressive bone metastases are a major source of morbidity in these patients, the bisphosphonates, pyrophosphate analogs that block bone destruction, were theorized to be a potentially useful treatment. Given the mechanism of action of the bisphosphonates, and the
lack of an impact of these drugs on PSA, a phase 3 trial of zoledronic acid was designed with “skeletal-related events” as the primary endpoint.\(^{27}\) Skeletal-related events were defined as pathologic bone fractures, spinal cord compression, surgery to bone, radiation therapy to bone, or a change of antineoplastic therapy to treat bone pain. By selecting a clinically relevant composite endpoint that was consistent with the mechanism of action of zoledronic acid, the investigators were able to demonstrate the beneficial effects of this treatment, resulting in approval by the FDA in 2003. The difficulty in interpreting the results of posttreatment bone scans and the potential importance of an adequate duration of exposure to novel therapies in order that they have a “chance to work” has also been highlighted by trials of novel therapies in CRPC. Atrasentan is a selective endothelin-A (ET\(_A\)) receptor antagonist that blocks or reverses the biologic effects of endothelin-1 (ET-1).\(^{28}\) The ET-1/ET\(_A\) axis is implicated in osteoclastic bone metastases, providing the rationale for developing atrasentan as a treatment for CRPC.\(^{29}\) Atrasentan was explored in a large phase 3 trial in men with CRPC with time to disease progression as the primary endpoint.\(^{30}\) Notably, the vast majority of patients progressed radiographically on the first posttreatment bone scan, without concomitant clinical progression, and were taken off study. The trial did not demonstrate an improvement in time to disease progression with atrasentan, which was perhaps in part related to an inadequate duration of exposure to the study drug.

Recognizing the lessons from several additional years of clinical trials in CRPC, and armed with a better understanding of the biology and natural history of prostate cancer, the Prostate-Specific Antigen Working Group reconvened to form the Prostate Cancer Working Group 2 (PCWG2).\(^{31}\) The PCWG2 updated eligibility and outcome measures for clinical trials in CRPC in an effort to maximize the ability of phase 2 trials to select promising therapies to move forward for definitive testing. Several critical recommendations by the PCWG2 have contributed to the successful development of new therapies for CRPC over the last 5 years, including 1) a major shift in emphasis from reliance on posttreatment changes in PSA to time-to-event endpoints; 2) a proposal for at least 12 weeks of treatment to ensure adequate exposure to a novel therapy; 3) a requirement for at least 2 new bone lesions to qualify for disease progression; and 4) a requirement for confirmation of bone scan progression on a subsequent bone scan to rule out tumor “flare,” progression that might have occurred before or just shortly after initiation of the study treatment, and nonspecific bone scan changes not truly indicative of metastatic disease.

**Redefining Hormone-Refractory Disease**

Prostate cancer that progresses despite castrate levels of serum testosterone has been historically referred to as “hormone-refractory” or “androgen-independent” disease. Among the most significant advances in prostate cancer over the past decade has been the realization that these tumors are not in fact hormone refractory, but may instead be hormone ultratensitive.\(^{32}\) Several mechanisms have been identified that account for the ability of prostate cancers to progress despite castration, including adrenal and intratumoral androgen synthesis, amplifications of the androgen receptor (AR), mutations of the AR, increased expression of AR coactivators, ligand-independent AR splice variants, and epigenetic modifications. These discoveries have led to a corresponding change in the terminology for this clinical state, now known as CRPC.\(^{33}\) The impact of this simple change in terminology should not be underestimated, as it has provided the context for the development of a new generation of “hormonal” therapies for the treatment of CRPC.

**A New Generation of Therapies That Improve Outcomes in CRPC**

With the historical challenges to drug development in CRPC as a backdrop, it is quite remarkable that 4 novel therapies have been approved by the FDA for the treatment of CRPC in just the past few years (sipuleucel-T, cabazitaxel, denosumab, and abiraterone), with additional drugs demonstrating promising results in late-stage clinical testing (Table 1).

**Sipuleucel-T**

Based on the presence of organ-specific antigen expression in the prostate, and the relatively indolent growth of prostate cancer compared with other solid tumors, immune-based approaches for the treatment of prostate cancer have long been of interest. Sipuleucel-T is an autologous active cellular immune therapy designed to elicit an immune response against prostatic acid phosphatase.\(^{34}\) The preparation and administration of sipuleucel-T involves leukopheresis to collect peripheral blood mononuclear cells (PBMCs) from patients, the culture of PBMCs (including dendritic cells) ex vivo with the PA2024 fusion protein (prostatic acid phosphatase linked to granulocyte-macrophage–colony-stimulating factor), and infusion of the resulting product back into patients. The precise mechanism of action of sipuleucel-T is unclear, and whether the clinical effects are related to the infusion of antigen-loaded dendritic cells, versus a nonspecific stimulation of the immune system, remains to be further elucidated.

Three randomized trials of sipuleucel-T for the treatment of CRPC have been performed, enrolling a total of 737 patients. These studies have generally included men who are chemotherapy-naive and asymptomatic or minimally symptomatic. In an integrated analysis of the initial 2 phase 3 trials (n = 225 patients), although the primary endpoint of an improvement in time to disease progression was not met, patients randomized to treatment with sipuleucel-T demonstrated a 33% reduction in the risk of death
(hazard ratio [HR], 1.50; 95% CI, 1.10–2.05 [P = .011]).\textsuperscript{35} Adverse events were primarily grades 1 to 2 and included chills, fever, headache, and fatigue (grading determined according to the National Cancer Institute Common Toxicity Criteria, version 2.0).

As both of these small phase 3 trials demonstrated an improvement in overall survival without meeting their primary endpoints of improving time to disease progression, the IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) study, which was adequately powered to detect an improvement in overall survival, was initiated.\textsuperscript{36} IMPACT enrolled 512 patients with asymptomatic or minimally symptomatic CRPC and randomized patients 2:1 to 3 infusions of sipuleucel-T administered every 2 weeks versus reinfusion of PBMCs alone on the same schedule. The majority of patients had primary tumors with Gleason scores ≤ 7, an eligibility criterion in the initial design of the trial that was later removed. Posttreatment declines in PSA and objective changes in metastatic disease were uncommon after treatment with sipuleucel-T; however, PSA values were only checked every 16 weeks and posttreatment PSA declines may have been missed. At a median follow-up of 34.1 months, the median survival was 4.1 months longer in the group treated with sipuleucel-T (25.8 months) than in the placebo group (21.7 months). The adjusted HR for death in the group treated with sipuleucel-T compared with the placebo group was 0.78 (95% CI, 0.61–0.98), representing a relative reduction in the risk of death of 22% (P = .03). Based on these results, sipuleucel-T was approved by the FDA for the treatment of asymptomatic or minimally symptomatic CRPC in 2010.

Because of a disconnect between time to disease progression and overall survival observed in these trials, there has been speculation that an imbalance in postprotocol treatment, as well as other factors, may have influenced the results.\textsuperscript{37} In an exploratory analysis, the impact of treatment with sipuleucel-T on outcomes remained consistent after adjusting for postprotocol use of docetaxel.\textsuperscript{36}

The sipuleucel-T experience highlights yet another important lesson in drug development and trial design in CRPC, particularly when considering agents with potential immune–related mechanisms of action. Such therapies may take months, or even years, to result in antitumor activity and even traditional time-to-event endpoints such as time to disease progression may not adequately screen for clinical benefit. Notably, an identical disconnect between lack of improvement in time to disease progression and improvement in overall survival has been observed in a randomized trial of the PROSTVAC-VF vaccine (BN ImmunoTherapeutics Inc, Mountain View, Calif).\textsuperscript{38}

**Cabazitaxel**

Cabazitaxel is a semisynthetic taxane from a single diastereoisomer of 10-deacetyl baccatin III and derived from the needles of various Taxus species. Cabazitaxel binds to tubulin and inhibits microtubule depolymerization and cell division, resulting in cell cycle arrest. Cabazitaxel was selected for clinical testing due to its poor affinity for the adenosine triphosphate (ATP)-dependent drug efflux pump P-glycoprotein \textsuperscript{1,39,40} and its greater blood-brain barrier penetration \textsuperscript{41} compared with paclitaxel and docetaxel. Cabazitaxel has demonstrated superior in vitro cytotoxicity compared with docetaxel in several murine and human cancer cell lines.\textsuperscript{39}

Given the promising results reported in the small cohort of patients with CRPC in a phase 1 trial of cabazitaxel, a randomized, multicenter, multinational, phase 3 trial (TROPIC [Treatment of Hormone-Refractory Metastatic Prostate Cancer Previously Treated with a Taxotere–Containing Regimen]) was initiated comparing cabazitaxel with mitoxantrone in patients with CRPC who had progressed despite docetaxel–based chemotherapy.\textsuperscript{42} A total of 755 patients were randomly assigned to either cabazitaxel at a dose of 25 mg/m\textsuperscript{2} intravenously over 1 hour or mitoxantrone at a dose of 12 mg/m\textsuperscript{2} intravenously over 15 to 30 minutes on day 1 of each 21-day cycle, with prednisone administered at a dose of 10 mg daily. Adverse events with cabazitaxel included neutropenia (94%), anemia (97%), and thrombocytopenia (47%), and 8% of patients experienced neutropenic fever. The most common nonhematologic toxicities observed in the cabazitaxel arm included diarrhea (47%) and fatigue (37%); peripheral neuropathy was rare. At median follow-up

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**TABLE 1. Recent Randomized Phase 3 Trials of Novel Therapies for CRPC**

| TRIAL                        | EXPERIMENTAL ARM       | CONTROL ARM         | POPULATION                        | MEDIAN SURVIVAL | P       |
|------------------------------|------------------------|---------------------|-----------------------------------|-----------------|---------|
| IMPACT                       | Sipuleucel-T           | Placebo             | Asymptomatic or minimally symptomatic, CRPC | 25.8 mo vs 21.7 mo | .03     |
| TROPIC                       | Cabazitaxel plus prednisone | Mitoxantrone plus prednisone | Docetaxel-treated, CRPC             | 15.1 mo vs 12.7 mo | < .0001 |
| COU-301\textsuperscript{1}  | Abiraterone plus prednisone | Placebo plus prednisone | Docetaxel-treated, CRPC             | 14.8 mo vs 10.9 mo | < .001  |
| AFFIRM                       | MDV3100                | Placebo             | Docetaxel-treated, CRPC             | 18.4 mo vs 13.6 mo | < .0001 |
| ALSYMPCA                     | Alpharadin (radium-223 chloride) | Placebo             | Docetaxel-treated, CRPC             | 14 mo vs 11.2 mo  | .0018   |

CRPC indicates castration-resistant prostate cancer; IMPACT, Immunotherapy for Prostate Adenocarcinoma Treatment; TROPIC, Treatment of Hormone-Refractory Metastatic Prostate Cancer Previously Treated with a Taxotere–Containing Regimen; ALSYMPCA, Alpharadin in SYMptomatic Prostate CaNcer.
of 12.8 months, an improvement in overall survival was demonstrated for the cabazitaxel arm compared with the mitoxantrone arm (15.1 months vs 12.7 months; HR, 0.70 [P < .0001]). In June 2010, cabazitaxel was approved by the FDA for the treatment of men with metastatic CRPC who were previously treated with docetaxel-based therapy.

Denosumab
Although bone metastases in prostate cancer are predominantly osteoblastic, several lines of evidence support a major role for excess osteoclastic activity in inducing bone destruction. Receptor activator of nuclear factor kappa-B ligand (RANKL) is a driver of osteoclast function and is upregulated in coculture of prostate cancer cells with osteoblasts. Inhibition of RANKL in an in vivo prostate cancer model prevented osteoclast-mediated bone destruction. Denosumab is a first-in-class human monoclonal antibody against RANKL.

A phase 3 study randomized 1904 patients with CRPC to denosumab at a dose of 120 mg subcutaneously versus zoledronic acid at a dose of 4 mg intravenously every 4 weeks. The primary endpoint of this study, similar to the study that established the role of zoledronic acid in CRPC, was the time to first on-study skeletal-related event. The median time to first on-study skeletal-related event was 20.7 months (95% CI, 18.8 months-24.9 months) in the denosumab arm compared with 17.1 months (95% CI, 15.0 months-19.4 months) in the zoledronic acid arm (HR, 0.82; 95% CI, 0.71-0.95 [P = .008]). Hypocalcemia occurred more commonly on the denosumab arm and osteonecrosis of the jaw occurred infrequently on both arms (1%-2%). These results led to the FDA approval of denosumab for the treatment of patients with CRPC metastatic to the bone in 2010.

Abiraterone
Abiraterone is an oral inhibitor of CYP17, a cytochrome p450 complex involved in adrenal steroid synthesis. Unlike ketoconazole, abiraterone is both selective and extremely potent. Recently, the importance of CYP17 in intratumoral androgen biosynthesis, in addition to adrenal androgen synthesis, has been suggested. In an analysis of patients with CRPC undergoing bone marrow aspiration, pretreatment CYP17 tumor expression was found to be significantly correlated with increased bone marrow aspirate testosterone concentration.

A phase 1 trial of abiraterone in patients with CRPC established proof of concept for CYP17 inhibition. In this study, patients received escalating doses between 250 and 2000 mg. Pharmacodynamic assessments revealed that posttreatment levels of serum testosterone and adrenal androgens rapidly declined after treatment, while mineralocorticoids increased. The latter effect was shown to be mitigated by the coadministration of eplerenone in this early phase trial, and with corticosteroids in later trials. Antitumor activity was observed in a large percentage of patients as manifested by declines in PSA, reductions in analgesic use, and regression of measurable disease. These promising findings were subsequently confirmed in larger phase 2 trials.

Two large phase 3 trials were subsequently initiated in docetaxel-resistant (COU-301) and chemotherapy-naive (COU-302) patients, although only the results of the former trial have been reported. COU-301 randomized 1195 patients with docetaxel-resistant CRPC, in a 2:1 fashion, to abiraterone at a dose of 1000 mg daily plus prednisone at a dose of 5 mg twice daily versus prednisone alone. Abiraterone was well tolerated, with mineralocorticoid-related adverse events being the most prominent, including fluid retention, hypertension, and hypokalemia. The survival data were unblinded at the interim analysis due to results exceeding the preplanned criteria for study termination. Overall survival was longer in the group of patients treated with abiraterone plus prednisone than in those receiving placebo plus prednisone (14.8 months vs 10.9 months; HR, 0.65; 95% CI, 0.54-0.77 [P < .001]). Based on these results, abiraterone was approved by the FDA in 2011. Abiraterone represents the first hormonal therapy to be approved in the postchemotherapy setting for CRPC.

MDV3100
Among the most frequent changes in AR signaling that contribute to the progression of prostate cancer despite castrate levels of serum testosterone are amplification or overexpression of the AR. AR overexpression shortens tumor latency in castrate mice and confers resistance to bicalutamide. MDV3100 is a novel antiandrogen selected for clinical development based on significant preclinical activity, even in the setting of AR amplification. Compared with bicalutamide, MDV3100 has greater affinity for the AR; lacks agonist effects; and, in addition to inhibiting ligand binding to the AR, also inhibits AR nuclear translocation.

A phase 1 to 2 study of MDV3100 was performed in patients with progressive CRPC. Patients were treated with escalating doses of daily oral MDV3100; antitumor activity was observed at all dose levels, and treatment was generally very well tolerated. At the highest dose levels studied (≥ 360 mg/day), 2 patients experienced witnessed seizures and one patient experienced a possible seizure; a dose of 240 mg daily was selected for further study. In the phase 2 portion of the study, 56% of patients achieved a > 50% posttreatment decline in PSA, 22% of patients demonstrated a regression of measurable disease, and circulating tumor cell counts converted from unfavorable to favorable in 49% of patients.
Notably, positron emission tomography imaging with \(18\)F-fluoro-5alpha-dihydrotestosterone revealed decreased binding of androgen to the AR, confirming the proposed mechanism of action. The most common adverse events (grade \(< 2\)) were nausea, constipation, diarrhea, and anorexia.

Two randomized, placebo-controlled, phase 3 trials were subsequently initiated, evaluating the efficacy of MDV3100 in patients with CRPC in the predocetaxel (PREVAIL) and postdocetaxel (AFFIRM) settings, respectively. Both trials have completed accrual. The preliminary results of the AFFIRM trial were reported in a press release in November 2011 and subsequently presented at the American Society of Clinical Oncology symposium on genitourinary cancers in 2012. The study was closed early by the independent data monitoring committee after meeting the prespecified interim efficacy stopping criteria. In this study, 1199 men with docetaxel-treated CRPC were randomized 2:1 to MDV3100 versus placebo. There was a significant increase in the percentage of patients achieving a >50% posttreatment decline in PSA with MDV3100 versus placebo (54% vs 1.5%; \(P < .0001\)) and a significant increase in regression of measurable disease (28.8% vs 3.8%; \(P < .0001\)). Treatment was generally well tolerated with numerically more adverse events and serious adverse events noted in the placebo group compared with the treatment arm. The estimated median survival for men treated with MDV3100 was 18.4 months compared with 13.6 months for men treated with placebo, resulting in a 37% reduction in the risk of death (HR, 0.631; \(P < .0001\)).

**Alpharadin**

Bone-targeting radiopharmaceuticals have long been of interest for use in the treatment of advanced prostate cancer, given the predominance of metastases to the bone and associated morbidity. Bone-targeting radiopharmaceuticals (strontium-89, samarium-153-ethylene diamine tetramethylene phosphonate [samarium-153-EDTMP]), using a variety of radioisotopes, have previously demonstrated the ability to effectively palliate pain in men with CRPC, although only more recently have data suggested a potential survival advantage with the use of these therapies.58-60 Alpharadin (radium-223) uses alpha radiation to exert its anticancer effects.51 A potential advantage of an alpha-particle-emitting radionuclide, compared with conventional bone-seeking radiopharmaceuticals that use beta-particles, is the short range of action of <100 \(\mu\)m. Therefore, the use of alpharadin may allow much more targeted delivery of radiation to bone metastases while sparing the bone marrow, which has been a limiting toxicity of the beta-emitters.

A randomized phase 2 study evaluated alpharadin versus placebo in 64 men with CRPC.62 There were no treatment discontinuations due to hematologic toxicity, and no evidence of cumulative toxicity, with repeated doses of alpharadin. There was a significant improvement in serum bone markers with alpharadin treatment, the study’s primary endpoint. Intriguingly, the median overall survival was 65.3 weeks for alpharadin versus 46.3 weeks for placebo (HR, 2.1; \(P = .017\)).

Based on these promising results, the phase 3 ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) trial was initiated. This trial randomized 922 patients with CRPC and bone metastases (who had progressed on, refused, or were deemed ineligible for docetaxel) 2:1 to alpharadin (6 intravenous administrations separated by 4-week intervals) versus placebo. Patients were required to have at least 2 bone metastases on bone scan and symptomatic disease was defined as the regular use of analgesic medication and/or external beam radiation therapy for bone pain within 12 weeks of enrollment. The primary endpoint of the study was overall survival. The results of ALSYMPCA were presented at the 2011 European Multidisciplinary Cancer Congress in Stockholm, Sweden.63 Treatment with alpharadin was associated with a median overall survival of 14 months versus 11.2 months with placebo (HR, 0.695; \(P = .00185\)). Furthermore, patients treated with alpharadin had a median time to first skeletal-related event of 13.6 months compared with 8.4 months in the placebo group. Treatment with alpharadin resulted in only mild myelosuppressive effects, with anemia as the most common hematologic toxicity. Alpharadin has received Fast Track designation by the FDA.

**Cabozantinib**

Peripheral blood markers of tumor angiogenesis have been correlated with poor outcomes in patients with CRPC, contributing to the rationale for exploring antiangiogenic agents in clinical trials.64 Unfortunately, approaches including the addition of the antivascular endothelial growth factor antibody bevacizumab to docetaxel or single-agent therapy with the small molecular inhibitor of the vascular endothelial growth factor receptor (VEGFR) sunitinib have failed to improve patient survival.65,66 Cabozantinib is a small molecule inhibitor of multiple receptor tyrosine kinases including RET, MET, VEGFR2/kinase insert domain receptor (KDR), and KIT. In normal prostate tissues, hepatocyte growth factor (HGF), the ligand for MET, modulates growth, cell adhesion, and migration and plays a role in angiogenesis and the inhibition of apoptosis.67 aberrant expression of HGF has been shown to promote tumor growth and progression in preclinical models and increased peripheral blood levels of HGF have been correlated with poor outcomes in patients with prostate cancer.68,69 Upregulation of MET has been demonstrated after castration of rats and MET overexpression has been shown to be more common in metastatic sites compared with primary prostate cancer samples.70
Based on the rationale for cotargeting VEGFR and MET in a variety of solid tumors, a novel approach was pursued in the clinical development of cabozantinib. An adaptive randomized discontinuation study was initiated, enrolling patients with a variety of malignancies including CRPC, pancreatic cancer, hepatocellular cancer, gastric cancer, melanoma, breast cancer, non-small cell lung cancer, small cell lung cancer, and ovarian cancer. Patients received cabozantinib at a dose of 100 mg orally daily. After 12 weeks of treatment, a restaging evaluation was performed. Patients with a complete or partial response continued cabozantinib treatment, those with progressive disease were withdrawn from the study, and those with stable disease were randomized to continue treatment versus receive placebo. Primary endpoints included the objective response rate during the “lead-in” phase and the progression-free survival during the randomization phase, and these endpoints were evaluated within each tumor type.

Objective antitumor activity with cabozantinib was observed among several tumor types. The preliminary results of the subset of patients with CRPC (n = 171) were presented at the 2011 American Society of Clinical Oncology annual meeting. All patients had measurable disease and 87% had bone metastases. Of the 171 patients enrolled, based on the 12-week restaging evaluation, 79 patients continued open-label therapy, 31 patients were randomized, and 61 patients came off study (25 of whom came off study due to an adverse event). Randomization was discontinued after 122 patients were enrolled based on early evidence of clinical benefit. Strikingly, among patients with bone metastases, 76% experienced a partial or complete disappearance of bone metastases on bone scan. While the mechanism of these rapid and marked bone responses are under further investigation, there was a correlation between bone scan improvement and improvement in pain. In fact, among patients who had been taking narcotics for bone pain, 67% had a reduction in pain and 56% decreased or stopped pain medication. Although only 7 patients (4%) met the criteria for a confirmed objective response in measurable disease, 75% demonstrated some degree of reduction in tumor size. Of the 31 patients undergoing randomization, the median progression-free survival was 21 weeks with cabozantinib versus 6 weeks with placebo (HR, 0.13; P = .0007). Adverse events were similar to other small molecules targeting the VEGFR; any grade fatigue occurred in 63%, diarrhea in 46%, hand-foot syndrome in 27%, and hypertension in 19% of patients. Thirteen patients (8%) developed deep venous thromboses and 2 patients (1%) developed gastrointestinal perforations. Approximately one-half of the patients required one or more dose reductions.

Additional trials of cabozantinib have been initiated (ClinicalTrials.gov identifiers NCT01428219 and NCT01347788), integrating biopsies of metastatic bone lesions, in an effort to further define the mechanism of the rapid improvement in lesions on bone scan. In addition, a randomized phase 3 trial of cabozantinib versus mitoxantrone in patients with CRPC is planned.

Current Status of Treatment for CRPC
With multiple new options available for the treatment of CRPC, in the absence of data regarding the appropriate sequencing of therapies, most treatment decisions in daily clinical practice are based on practical factors including patient preference, functional status/comorbidities, and economic considerations. For instance, given the mechanism of action of sipuleucel-T, and the lack of frequent objective responses with this therapy, patients with chemotherapy-naïve, slowly progressive, metastatic prostate cancer are generally considered the most appropriate candidates. Along similar lines, the use of postdocetaxel treatment with cabazitaxel versus abiraterone may be influenced by the duration of control on prior hormonal therapies, exposure to prior ketoconazole, functional status, and rate of disease progression. Many patients will ultimately be exposed to several, if not all, of these novel therapies in succession until evidence-based guidelines and biomarkers are available to refine the selection of therapies.

Future Directions: Combination Versus Sequential Therapy
With the development of multiple new agents with diverse mechanisms of action for the treatment of CRPC, the optimal sequencing of drugs for clinical use becomes a major unanswered question. In addition, following the traditional paradigm in oncology since the development of the first successful multiagent drug regimens in leukemia, the issue of combining potentially non–cross-resistant drugs, with seemingly nonoverlapping toxicity profiles, is raised. While such approaches are attractive, failures with combination regimens over the past few years highlight the need to proceed only based on the soundest preclinical rationale. Examples of rational approaches to combination therapy include trials being initiated that target both AR signaling and phosphoinositide 3-kinase (PI3K)–AKT signaling, based on preclinical studies demonstrating critical cross-talk between these pathways. Other studies are examining the potential for a negative impact of the coadministration of novel therapies for CRPC. For instance, a trial is exploring the sequential versus concurrent use of abiraterone and prednisone plus sipuleucel-T based on the potential for the concurrent use of corticosteroids to blunt the immune response to sipuleucel-T. Finally, the economic impact of this host of novel, expensive therapies can no longer be ignored, and the true value of combination and sequential approaches will need to be explored in detail.
The past several decades have witnessed an improved understanding of CRPC in concert with a better idea of how to appropriately develop drugs for this disease in the clinic. The fruits of these efforts are unmistakable. The challenge now is to continue this pace of progress for this heretofore incurable disease, while simultaneously demonstrating the effectiveness and value of the current generation of treatments.

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