**Systemic Therapy for Castration-resistant Prostate Cancer: Novel Agents and New Standards**

By Kim N. Chi, MD, Charles G. Drake, MD, and Thomas W. Flaig, MD

**Overview:** Systemic therapy for castration-resistant prostate cancer (CRPC) has advanced significantly over the past decade, fueled by the increased understanding of the mechanisms underlying prostate cancer progression, including persistent androgen receptor (AR) activation, cell survival, proliferation, cell signaling, angiogenesis, bone metastases, immunotherapy, and drug resistance. Mitoxantrone, zolodronic acid, and docetaxel have been standard treatments for CRPC based on their benefits for pain symptoms, skeletal-related events (SREs), and overall survival, respectively. In the past year, we have seen four new therapies representing a diversity of approaches with phase III data to support their use for patients with CRPC: sipuleucel-T is a cellular immune therapy shown to improve survival in minimally symptomatic patients; cabazitaxel is a microtubule-directed cytotoxic agent that, when combined with prednisone, was the first agent to show an overall survival mortality benefit in CRPC after progression with docetaxel chemotherapy; denosumab is a fully human monoclonal antibody against receptor activator of nuclear factor-κB (RANK)-ligand and shows superior activity to zoledronic acid in delaying the time to SREs in CRPC patients with bone metastases; and finally, abiraterone acetate is a selective CYP17 inhibitor associated with a survival advantage in patients with CRPC progressing after docetaxel chemotherapy. Ongoing and planned studies of these agents in other prostate cancer disease states and a plethora of clinical trials of novel agents as single agents and in combinations continues to drive the rapid evolution of systemic treatment for CRPC.

**AR Activation**

CRPC has been previously termed “hormone refractory” or “androgen independent.” Accumulating evidence suggests these terms are not appropriately descriptive, as progression of prostate cancer after chemical or surgical castration frequently remains dependent on AR signaling. Mechanisms underlying the development of CRPC have been increasingly understood, a number of new treatment strategies have been developed including those targeting the AR activation, growth factor signaling, survival pathways, and immune system (Table 1). Recently, phase III trials testing novel agents against a diversity of targets have reported improved outcomes in patients with CRPC that have expanded treatment choices (Table 2). This paper reviews the rationale for new systemic therapies currently in clinical evaluation with an emphasis on those in late-stage trials and describes the evolving standard of care for patients with CRPC.

**Novel Targets, Novel Agents**

**AR Activation**

CRPC has been previously termed “hormone refractory” or “androgen independent.” Accumulating evidence suggests these terms are not appropriately descriptive, as progression of prostate cancer after chemical or surgical castration frequently remains dependent on AR signaling. Mechanisms underlying the development of CRPC have been postulated implicating persistent AR signaling, including extra-gonadal production of androgens that form malignant prostate tissues and amplification with increased expression of the AR resulting in a hypersensitive pathway. Ligand independent, constitutively active AR splice variants have also been described. It has long been observed that patients with CRPC can respond to second-line hormonal maneuvers, and development of more potent inhibitors of extra-gonadal androgen synthesis and AR antagonists have been areas of active research.

The CYP17 enzyme has dual function as both a 17α-hydroxylase and a C17,20-lyase, and both of these functions are required to synthesize androgens. Abiraterone acetate and TAK-700 are inhibitors of CYP17 currently in clinical development. Phase I and II studies of abiraterone acetate have demonstrated good tolerance with mechanism-based side effects of mineralocorticoid excess (hypertension, hypokalemia, edema) as inhibition of CYP17A1 decreases cortisol levels resulting in a compensatory increase in adrenocorticotropic hormone (ACTH) and a subsequent increase in deoxycorticosterone and corticosterone. These effects could be ameliorated with concomitant administration of mineralocorticoid antagonists or low-dose corticosteroids to suppress ACTH. Biologic activity has also been observed with abiraterone acetate with further suppression of serum testosterone in patients already receiving castration therapy, and clinical responses seen in terms of prostate-specific antigen (PSA) declines and objective responses. A phase III study of abiraterone acetate in patients with CRPC progressing after docetaxel has recently been reported, demonstrating improved overall survival (OS). A second phase III study in patients who are chemotherapy-naive (Clinical Trials.gov identifier: NCT00887198) has completed accrual and results are pending for the primary endpoints of progression-free survival (PFS) and OS. TAK-700 has similarly demonstrated tolerability and activity in phase I/II studies. Phase III trials in patients who have had prior docetaxel chemotherapy (NCT01198257) or are chemotherapy naive (NCT01198244) are now accruing.

MDV3100 is a potent AR antagonist that prevents nuclear translocation and DNA binding of AR, and displays no agonistic activity. In a phase I/II study, MDV3100 showed activity both in patients who are chemotherapy-naive and those who have had chemotherapy (57% and 45% of patients experienced a PSA decline of ≥50%, respectively). Radio-
graphic control was observed in 74% of patients with evaluable soft tissue lesions and in 62% of those with bone lesions. Adverse events at higher doses necessitating dose reductions included rash, seizure, and fatigue. A placebo-controlled phase III trial of MDV3100 in patients with CRPC progressing after docetaxel therapy has completed accrual (NCT00974311). A second phase III trial of MDV3100 has also been initiated in patients who are chemotherapy naive (NCT01212991).

**Clusterin**

Clusterin is an adenosine triphosphate–independent, stress-induced molecular chaperone protein similar to small heat shock proteins that protect cells from stress-induced protein misfolding, aggregation, and denaturation, and play roles in cellular signaling and transcriptional regulatory networks. Clusterin is overexpressed in various cancers, including prostate, and expression has been shown to increase after anticancer treatment. Clusterin overexpression is associated with antiapoptotic and prosurvival effects acting through mechanisms that include inhibition of endoplasmic reticulum stress, suppressing Bax-mediated apoptosis, and signaling through Akt.

**OGX-011** is a second-generation antisense oligonucleotide that targets clusterin mRNA and potently reduces clusterin expression. Phase I studies with OGX-011 have demonstrated tolerability and proof-of-principle biologic effects of clusterin expression inhibition in primary prostate tumors and serum of patients. In a randomized phase II study of patients with CRPC who are chemotherapy naive, treatment with OGX-011 (640 mg IV once weekly) plus docetaxel-prednisone demonstrated similar response rates in terms of PSA declines and measurable disease, but was associated with improved OS over docetaxel-prednisone alone on multivariate analysis (hazard ratio [HR] 0.50; 95%CI 0.29–0.87). In another randomized phase II study, the combination of OGX-011 with docetaxel-prednisone appeared superior in terms of PSA decline, pain response, and PFS compared with OGX-011 plus mitoxantrone-prednisone.
in patients who had progressed after receiving prior docetaxel therapy.\(^{15}\) Two phase III studies have been initiated with OGX-011 in patients with metastatic CRPC. One randomly selects patients who are chemotherapy naive to receive docetaxel-prednisone with or without OGX-011 (NCT01188187). The other study involves the same treatment arms but with a placebo control in patients undergoing docetaxel rechallenge after prior first-line docetaxel (NCT01083615).

**Angiogenesis**

Vascular endothelial growth factor (VEGF) signaling is a major mediator of angiogenesis and implicated in prostate cancer progression. Phase II evidence of enhanced clinical activity has been shown with bevacizumab, a monoclonal antibody inhibitor of VEGF-A, in combination with docetaxel-estramustine in patients with CRPC. However, a phase III study led by the Cancer and Leukemia Group B that evaluated docetaxel with or without bevacizumab did not demonstrate an OS benefit for the combination.\(^{16}\) Aflibercept (VEGF trap) is a fusion protein that incorporates portions of human VEGF receptor (VEGFR)-1 and VEGFR-2 fused to the constant region of human immunoglobulin G1 and potently binds to VEGF-A, VEGF-B, and placental growth factor. A phase III study of docetaxel-prednisone with aflibercept compared with docetaxel-prednisone as first-line chemotherapy has completed accrual and OS results have yet to be reported (NCT00519285).

Multitarget tyrosine kinase inhibitors (TKIs) active against VEGFR and other angiogenic and proliferative pathways have also been evaluated for the treatment of CRPC. Low levels of clinical activity have been observed in phase II studies of sunitinib, sorafenib, and cedirinib. However, discordant responses have also been described with these agents in the form of improved radiologic imaging despite increasing PSA.\(^{17}\) A phase III study evaluating sunitinib in patients with CRPC after failure on docetaxel was initiated but was closed prematurely because of futility for the OS primary endpoint (NCT00676650). Although disappointing for a VEGFR TKI approach, it may be that additional pathways need to be targeted. Promising initial results of a phase II study evaluating XL184, a VEGFR TKI that also targets the MET receptor, were recently reported demonstrating responses in pain symptoms, bone scans, and measurable disease, which appeared independent of PSA changes.\(^{16}\)

Thalidomide and its derivative, lenalidomide, have antiangiogenic and immunomodulatory properties. Early-phase studies in patients with prostate cancer have been performed with thalidomide and lenalidomide as single agents and in combination with various agents, such as docetaxel, GM-CSF, and ketoconazole, with clinical activity observed. A phase III placebo-controlled study of docetaxel and prednisone with or without lenalidomide in patients with CRPC is actively recruiting (NCT00988208).

**Sipuleucel-T**

Sipuleucel-T is an autologous cellular immunotherapy for asymptomatic CRPC that utilizes modified leukocytes to provide an immunotherapeutic process. Earlier application in the asymptomatic setting of CRPC who are chemotherapy naive or in the early stages of disease progression has also been evaluated for the treatment of CRPC. A phase III study of sipuleucel-T vs. placebo in patients with CRPC with bone metastases was defined by symptoms and imaging but not PSA elevation in men with metastatic prostate cancer and medical treatment settings.\(^{18}\) Serious vascular events and deep venous thrombosis was defined by symptoms and imaging but not PSA changes. Serious vascular events and deep venous thrombosis were more common in the treatment group compared with the placebo group (3% to 4% vs. 0%) as were grade 3 to 4 adverse events (38% vs. 10%). A phase III study is planned in patients with CRPC who are chemotherapy naive (NCT01234311).

**Src Family Kinase**

The Src family of nonreceptor tyrosine kinases are involved in signal transduction downstream of cell surface receptors—including EGFR, PDGFR, VEGFR, and integrins—and thus are associated with prostate cancer progression through multiple cellular processes, including differentiation, proliferation, adhesion, and migration. Src signaling is important for normal functioning of osteoclasts, bone resorption, and osteoblast proliferation and bone deposition, and implicated in bone metastases progression. Dasatinib is a TKI with activity against the Bcr-abl tyrosine kinase but also Src. Phase II trials using single-agent dasatinib in patients with CRPC have demonstrated minor PSA declines, however, decreases in bone turnover markers were observed.\(^{20}\) A randomized phase III study of docetaxel with or without dasatinib is being conducted (NCT00744497).

**Endothelins**

Endothelins (ET) are 21-amino acid peptides that are elevated in men with metastatic prostate cancer and mediators of the osteoblastic response of bone to metastatic disease. ET-1 preferentially binds to ET-A, which has been
associated with proliferation, antiapoptotic effects, and pain. Atrasentan is an orally bioavailable inhibitor of ET-A with biologic efficacy demonstrated in early studies; however, two phase III trials failed to show an improvement in time to progression (TTP) despite evidence of decreased bone turnover. Development of atrasentan in combination with docetaxel continues with a phase III trial conducted by the Southwest Oncology Group which has completed accrual (NCT00134056). Zibotentan is a more specific inhibitor of ET-A also in clinical testing. A randomized phase II trial assessing two doses of zibotentan compared with placebo showed no differences in the primary endpoint of progression, but an apparent OS benefit in favor of the zibotentan treatment arms did emerge.21 Consequently, three phase III trials were undertaken: zibotentan compared with placebo in patients with CRPC without metastases (Endothelin A Use [ENTHUSE] Study 15, NCT00626548), with bone metastases that have no/minimal associated symptoms (Study 14, NCT00554229), and in patients receiving docetaxel (Study 33, NCT00617669). A recent press release from the sponsor has indicated that the ENTHUSE Study 14 failed to meet its primary endpoint of OS.

Immunotherapy for Advanced CRPC

In April 2010, the United States Food and Drug Administration (FDA) approved the active cellular immunotherapy product sipuleucel-T for the treatment of men with asymptomatic or minimally symptomatic CRPC. This decision marked the first specific immunotherapy product (vaccine) approved for the treatment any solid tumor. Currently, two other immunotherapy reagents are advancing through phase III clinical trials for men with CRPC.

Sipuleucel-T

This autologous cellular product is in some ways very similar to a traditional dendritic cell vaccine approach. Briefly, a patient undergoes leukapheresis, and the resulting cells are transported to a central processing facility, where their monocytes are enriched through standard laboratory techniques and cultured for approximately 36 hours with a proprietary fusion protein (PA2024), coupling a target antigen (prostatic acid phosphatase [PAP]) to the cytokine (granulocyte-macrophage colony-stimulating factor [GM-CSF]). Although the exact immunologic mechanisms involved are still under investigation, current data show that GM-CSF activates and matures antigen-presenting cells in the culture, while at the same time targeting PAP to the resulting product is shipped back to the physician's office, where the cells are administered intravenously. This process is repeated three times, at 2-week intervals, over a total of 4 to 6 weeks. As might be imagined, the iterative nature of this process results in an increasingly potent product from an immunologic perspective; the second and third infusions show increasing evidence of monocyte and T-cell activation. Side effects are generally minimal—myalgias, fever, and fatigue are common, but grade 3 to 4 toxicity is rare.

The pivotal clinical trial that led to FDA approval was recently published.22 Over 500 patients were randomly selected 2:1 to receive either active vaccine product (sipuleucel-T) or a series of placebo infusions consisting of one-third of the leukapheresis product. The primary endpoint of the trial was OS. One controversial aspect of the trial design was the inclusion of a late-stage crossover (i.e., patients originally treated with placebo could receive active vaccine, prepared from frozen cells) on progression. The crossover design reflected the trial’s original TTP endpoint, which was modified as increasing evidence has shown that OS was more likely to reflect clinical benefit for immunotherapy agents.23,24 Despite the trial design, which was biased against detecting a survival benefit, phase III data revealed a significant OS benefit: 25.8 months for men initially treated with sipuleucel-T compared with 21.7 for men in the placebo group (HR = 0.78; p = 0.03). As predicted, TTP was not significantly different between the two groups.

Several questions regarding sipuleucel-T remain unresolved. The first involves the precise mechanism of immunologic action invoked. Correlative biologic studies showed clear evidence that patients developed a T-cell–mediated immune reaction against the PAP/GM-CSF fusion protein, but responses against native PAP were comparatively less frequent. Antibody response against PAP may also play a role in the improved survival noted in treated patients: anti-PA2024 antibodies were detected in 66% of patients on the active treatment arm, compared with only 2.9% of the placebo group. From a clinical viewpoint, it is also difficult to understand how an OS benefit can be mediated without some evidence of objective response. Current immunologic thinking suggests that the rate of disease progression may be diminished by active immunotherapy, resulting in an improved survival without frank disease shrinkage.25 The observation that immunotherapy reagents generally appear to be more functional in patients with a lower disease burden may also play a result in these positive results, as the trial enrollment was limited to patients with either asymptomatic or minimally symptomatic disease.

Anti-CTLA-4

A fully human monoclonal antibody that blocks the interaction between cytotoxic T lymphocyte antigen 4 (CTLA-4) and its ligands is currently being evaluated in randomized phase III trials in prostate cancer. This agent, ipilimumab, has a different mechanism of action than a cancer vaccine, functioning by blocking a negative signal transmitted to otherwise functional tumor-specific killer lymphocytes (effectively taking off the brakes of a pre-existing antitumor immune response). A recent phase III trial of ipilimumab in patients with metastatic melanoma documented a clear survival advantage for treated patients representing the first randomized trial in this disease to achieve this milestone.26 Unlike cancer vaccines, ipilimumab has a substantial (20% to 30%) incidence of autoimmune side effects, most notably inflammation of the gastrointestinal tract, manifesting as colitis, an attribute which may limit widespread applicability in asymptomatic patients with cancer.

Phase I and II data showed some evidence of clinical responses, both as a single agent as well as in combination with radiation therapy.27 An interesting phase I trial combined this ipilimumab with GM-CSF in an effort to stimulate endogenous antigen–presenting cells, and radiologic and PSA responses were observed.28 Based on these data, two phase III trials have been initiated. The first, initiated
in 2009, will evaluate ipilimumab in patients who have progressed during or after docetaxel chemotherapy, who has a primary endpoint of OS (NCT00861614). One interesting aspect of this study is the inclusion of a low-dose of radiation to a bone lesion to prime or initiate an immune response through the putative release of tumor antigens from dying tumor cells. This concept is well supported by preclinical data but has yet to be formally evaluated in a randomized clinical trial setting. A second phase III trial of ipilimumab focuses on a less advanced patient population, men with metastatic CRPC who have not yet been treated with chemotherapy (NCT01057810).

PROSTVAC-VF

Unlike sipuleucel-T, PROSTVAC-VF is a generic vaccine product that does not require personalized manufacturing. This agent is based on a viral backbone, incorporating the target antigen (PSA) as part of a vaccinia virus backbone, similar to that used in smallpox vaccines. In addition to the target antigen, PROSTVAC-VF further incorporates three additional molecules in effort to further stimulate the immune response. This agent has been evaluated in an extensive series of single-agent and combination trials, which, taken together, document clear evidence for tolerability and some evidence for efficacy. The most interesting data regarding PROSTVAC-VF involved a randomized phase II trial very similar in design to the pivotal trial of sipuleucel-T. One hundred and twenty five men were randomly selected in a 2:1 manner to receive either PROSTVAC-VF or placebo. The primary endpoint, TTP, was not met at the time of an initial analysis. However, longer follow-up showed an OS benefit (25.1 vs. 16.6 months; HR = 0.56; p = 0.006). The hypothesis that PROSTVAC-VF improves OS in men with asymptomatic CRPC will be tested in a phase III trial planned to initiate in 2011.

Although space limitations prohibit a discussion of additional immunotherapy approaches, as well as the concept of combining immunotherapy with either conventional therapy or other immunotherapy agents, interested readers are directed to topical reviews for additional information.

**Systemic Therapy in Advanced CRPC: New Standards in 2011**

In the last year, new systemic treatment approaches for CRPC have reported positive results in the phase III setting. These new agents consist of a heterogeneous group, including sipuleucel-T, cabazitaxel, denosumab, and abiraterone acetate. The availability of these medical treatments—now each with positive results in the phase III setting—will substantially change the treatment approach to CRPC.

**Cabazitaxel**

In 2004, docetaxel with prednisone was approved for use in CRPC on the basis of an approximately 2.5-month survival advantage over mitoxantrone-prednisone. Importantly, docetaxel additionally improved global and pain-based quality-of-life measures when compared with mitoxantrone, and docetaxel-prednisone became a standard of care treatment for the first-line treatment of metastatic CRPC.

Cabazitaxel is a microtubule-targeted agent, with a mechanism of action similar to docetaxel, having in vitro activity in taxane-resistant models. In 2010, a randomized, phase III trial was conducted of cabazitaxel 25 mg/m² compared with mitoxantrone 12 mg/m² every 3 weeks, with all subjects also receiving prednisone 10 mg daily. The median survival was 15.1 months compared with 12.7 months in the cabazitaxel and mitoxantrone groups, respectively (HR = 0.70; p = 0.0001). The median PFS also favored cabazitaxel (2.8 vs. 1.4 months). Comparing the adverse event profile of these agents, cabazitaxel was associated with more bone marrow suppression. Grade 3 or higher neutropenia was noted in 82% of the patients treated with cabazitaxel compared with 58% of the patients treated with mitoxantrone; the incidence of febrile neutropenia was also higher with cabazitaxel (8% vs. 1%). Diarrhea was more common with cabazitaxel (47% vs. 11%), although only a small proportion was grade 3 or higher (6%). Death within 30 days of last treatment (excluding death from disease progression) was more common with cabazitaxel (18 vs. 3 subjects) with seven of these related to neutropenia and infection.

Cabazitaxel with prednisone was the first regimen to demonstrate an OS advantage in CRPC patients with progressive disease after docetaxel therapy and has been approved by the FDA for use in this setting. Special attention should be given to prevent dehydration from diarrhea and to consideration of G-CSF support in appropriate patients.

**Denosumab**

Bone health is a significant issue in advanced prostate cancer. SREs, including fracture, progressive bone pain, spinal cord compression, or the need for radiation therapy or surgery, are common in this setting. The causes of compromised bone health in CRPC are multifold: reduced bone mineral density (BMD) from castration, frequent glucocorticoid use, and purported biologic changes related to the cancer and bone metastases. The preservation of bone health entails a balance between osteoclast activity (bone resorption) and osteoblastic activity (bone formation). With both androgen-deprivation therapy (ADT) and factors mediated by the tumor itself, the equilibrium between osteoclastic and osteoblastic activity is altered, promoting SREs.

Zoledronic acid is a high potency bisphosphonate approved for use in CRPC patients with bone metastases. Its activity in this setting is through inhibition of osteoclastic activity, which is often pathologically increased in CRPC. Zoledronic acid at 4 mg intravenously every 3 weeks compared with placebo was associated with a reduction in the incidence of SREs in men with metastatic bone disease from CRPC (44% vs. 33%). A new osteoclast inhibitor, denosumab, is a fully human monoclonal antibody that binds to and inhibits the RANK-ligand, an important activator of osteoclastic activity that is upregulated in CRPC. As a fully human antibody, denosumab differs from zoledronic acid in that denosumab is administered subcutaneously with less concern for renal toxicity or for renal dose adjustments. Denosumab was approved by the FDA in 2010 for the prevention of SREs in patients with bone metastases from solid tumors.

Denosumab has been studied in men with nonmetastatic prostate cancer receiving ADT. In a double-blinded phase III trial, 1,468 subjects received either denosumab (60 mg) or placebo every 6 months. With 24 months of treatment, the BMD of the lumbar spine increased 5.6% with denosumab, compared with a loss of 1% of BMD with placebo (p < 0.001).
The incidence of vertebral fracture was also lower with denosumab (1.5% vs. 3.9%) at 36 months. In a second study, denosumab was compared to zoledronic acid in 1901 patients with bone metastases from CRPC.36 Denosumab significantly extended the time to the first on-study SRE (HR = 0.82; p = 0.008) with a median time of 20.7 compared with 17.1 months. Common side effects included hypocalcemia with an incidence of 13% and 6% in the denosumab and zoledronic acid arms, respectively. Osteonecrosis of the jaw was also observed in 2.3% of the denosumab group compared with 1.3% of the zoledronic acid group. There was no difference in PFS or OS.

**Abiraterone Acetate**

As discussed above, abiraterone acetate is a potent inhibitor of CYP17 and androgen synthesis. High-dose ketoconazole has also been used as a secondary hormonal maneuver, capitalizing on its known adrenal suppressive properties to decrease extragonadal androgen production.37 Ketoconazole differs from abiraterone acetate in that it is a less potent and less specific inhibitor of CYP17 and ketoconazole’s use is accompanied by significant off-target side effects. Abiraterone acetate has shown activity in both the pre- and postchemotherapy CRPC setting, as well as in patients previously exposed to ketoconazole, although perhaps at a lower rate of response.36

In 2010, the results of the phase III trial of abiraterone acetate in the postchemotherapy CRPC setting were announced.38 In this randomized, placebo-controlled trial, 1,195 men with metastatic CRPC with progression after docetaxel chemotherapy were given low-dose prednisone with or without abiraterone acetate daily. An increase in the median OS (10.9 vs. 14.8 months) was observed in the abiraterone acetate group (HR = 0.65; p < 0.0001). The time to PSA progression was also significantly improved with abiraterone acetate (6.6 vs. 10.2 months), as was the overall PSA response rate (38% vs. 10%). Although there were no dose-limiting adverse events in the phase I trial, toxicity related to mineralocorticoid excess (hypertension, peripheral edema, and hypokalemia) was observed. The most common adverse events included fluid retention (30.5% vs. 22.3%) and hypokalemia (17.1% [grade 3–4 in 3.8%] vs. 8.4%), each observed more commonly in the abiraterone acetate group.

**Conclusion**

Important advancements in the systemic treatment of CRPC have been recently made with a diversity of approaches. Overall survival benefits have been demonstrated with sipuleucel-T, cabazitaxel, and abiraterone acetate. In addition, denosumab has shown superior activity in delaying the time to an SRE in patients with CRPC who have bone metastases. Ongoing and planned studies of these agents in other prostate cancer disease states and a plethora of clinical trials of novel agents as single agents and in rational combinations will continue to drive the evolution of systemic treatment for CRPC.

**Authors’ Disclosures of Potential Conflicts of Interest**

<table>
<thead>
<tr>
<th>Author</th>
<th>Employment or Leadership Positions</th>
<th>Consultant or Advisory Role</th>
<th>Stock Ownership</th>
<th>Honoraria</th>
<th>Research Funding</th>
<th>Expert Testimony</th>
<th>Other Remuneration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim N. Chi</td>
<td></td>
<td>sanofi-aventis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thomas W. Flaig</td>
<td></td>
<td>Amgen</td>
<td></td>
<td></td>
<td>sanofi-aventis</td>
<td>Cougar Biotechnology, Medivation, sanofi-aventis</td>
<td></td>
</tr>
<tr>
<td>Charles G. Drake</td>
<td></td>
<td>AmplitImmune, Bristol-Myers Squibb, Dendreon</td>
<td>Amplimmune</td>
<td>IMER</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**REFERENCES**


12. Zoubeidi A, Chi K, Gleave M. Targeting the cytoprotective chaperone,


18. Smith DC, Spira A, Greve JD, et al. Phase 2 study of XL184 in a cohort of patients (pts) with castration resistant prostate cancer (CRPC) and measurable soft tissue disease. 22nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics. 2010; abstr 406.


