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The Role of Surrogate Markers in the Management of Men With Metastatic Castration-Resistant Prostate Cancer

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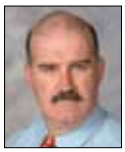

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Abstract: Over the past year, the treatment of metastatic castration-resistant prostate cancer (mCRPC) was dramatically altered with the introduction of several novel agents. One of these agents, the cancer immunotherapy sipuleucel-T, represents a major change in the treatment paradigm for patients with mCRPC. While immunotherapies such as sipuleucel-T are associated with a significant improvement in overall survival, many questions remain regarding their use. Specifically, there are questions as to which endpoints should be used to measure benefit with immunotherapy. Clinical trials of sipuleucel-T demonstrated that the traditional endpoints normally used in mCRPC trials, such as progression-free survival, are not good measures of response with immunotherapy. However, measurement of overall survival is difficult in the clinical trial setting. There is now a major interest in the identification of surrogate biomarkers of survival that could allow the benefit of novel agents to be more precisely determined. Many potential biomarkers have been identified, often from studies showing their prognostic potential. In this roundtable, experts discuss the role of biomarkers in measuring response to immunotherapy for men with mCRPC.

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Target Audience

This activity has been designed to meet the educational needs of oncologists and other healthcare professionals who treat patients with prostate cancer.

Statement of Need/Program Overview

Treatment options for metastatic castration-resistant prostate cancer (mCRPC) have recently expanded to include several novel agents. One of these agents is the cancer immunotherapy agent sipuleucel-T, which acts through a different mechanism than older prostate cancer treatments. While immunotherapies such as sipuleucel-T are associated with a significant improvement in overall survival, the traditional endpoints normally used in mCRPC trials, such as progression-free survival, are not good measures of response with immunotherapy. Thus, there is now a major interest in the identification of surrogate biomarkers of survival that could allow the benefit of novel agents to be more precisely determined. Many potential biomarkers have been identified, often from studies showing their prognostic potential. Clinicians need to be aware of these biomarkers in order to fully appreciate the results of recent clinical trials and to better implement immunotherapy in clinical practice.

Educational Objectives

After completing this activity, the participant should be better able to:

- Identify possible roles of surrogate markers in determining treatment efficacy in mCRPC
- Assess the impact and merit of immune system activation and immunotherapy in mCRPC
- Discuss biomarkers and their role in the assessment and treatment of patients with mCRPC

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Role of Surrogate Markers in Determining Treatment Efficacy

Andrew J. Armstrong, MD, ScM

A clear understanding of the distinction between prognostic, predictive, and surrogate biomarkers is essential for drug development in oncology. We will focus our discussion on these markers as they relate to metastatic castration-resistant prostate cancer (mCRPC). Given the number and increasing complexity of both novel and older agents approved in this disease (abiraterone acetate, sipuleucel-T, cabazitaxel, docetaxel, denosumab, radium-223, and MDV3100) and the number of agents in phase III testing, using biomarkers to identify patients who are responding or resistant to therapy and to enrich for patient populations most likely to benefit and not be harmed by therapy is important for the rational use and sequencing of these agents. Both prognostic and predictive factors can be used to group patients into relatively homogenous subsets based on outcome, but they differ in important ways.

Prognostic biomarkers are characteristics of either the disease or the patient that can be used to estimate the chance that a particular event will occur. For example, prognostic factors can be used to determine the chance of disease-related death, disease progression, or disease recurrence. When a prognostic factor is dependent on the disease, as in these examples, it is a function of the natural history of the disease itself. Determining a patient's prognosis is essential, as it impacts on decision-making and treatment selection.[1] Numerous prognostic factors have been established or investigated in mCRPC patients.

In contrast, **predictive biomarkers** are characteristics of either the disease or the patient that can be used to estimate the chance that a particular treatment will result in an improvement in a specific outcome, such as survival. For example, expression of the HER2 receptor in a breast cancer tumor is a predictive factor for the use of HER2-directed therapies, such as trastuzumab. In patients with mCRPC, baseline factors that can predict whether a certain therapy will be of benefit have not yet been established or validated; however, this is an area of active research and great promise.

Nomograms are tools that use a large number of these factors to estimate prognosis about an outcome. By incorporating various factors, nomograms can provide an accurate and quantifiable prognosis for an individual patient. Because they account for discordant prognostic values, nomograms are considered to be more powerful and precise than simple risk-group assignment, which may place a patient in an intermediate-risk or high-risk group based on a single poor prognostic factor.[1,2] Several dozen nomograms are now available for prostate cancer patients. These can be categorized according to disease state; as such, 3 are widely used in men with mCRPC.[1,3,4] The most frequently used prognostic nomograms for mCRPC include the Halabi nomogram, the Armstrong TAX 327 nomogram, and the Smaletz Memorial Sloan-Kettering nomogram.[5-7] However, these models cannot necessarily predict what therapy is most useful for a patient at a given time, in that they are not predictive models. Also, these models are not dynamic in nature, in that they do not provide updated prognostic information based on the response of a patient to a new therapy.

Surrogate Factors in mCRPC

Surrogate biomarkers go a step beyond prognostic and predictive factors and are really quite different in nature. A surrogate is an intermediate factor that occurs temporally between treatment and the endpoint of interest (such as survival). Surrogates can be defined statistically, but essentially they are factors that capture the true clinical benefit of an intervention. A true surrogate biomarker offers the advantage of replacing true outcome endpoints in a clinical trial; thus, surrogate factors are an important potential component in the rapid evaluation of new cancer therapeutics and the early identification of active agents for clinical testing in large-scale trials. In a seminal paper by Prentice in 1989, several criteria were established to help define a surrogate endpoint.[8] These criteria include the following: 1) the treatment significantly changes the endpoint; 2) the treatment significantly changes the surrogate; and 3) the full effect of treatment on the endpoint is explained through the effect of treatment on the surrogate. Beyond these criteria, others have shown the importance of quantifying the degree of surrogacy at both the trial level and across multiple trials of a variety of active agents with a range of mechanisms of action.[9]

A surrogate factor depends on the mechanism of action of a particular therapy. Surrogate factors can be statistically defined, and they are quantified according to the proportion of the treatment effect that is explained by the surrogate or

other measures such as the likelihood ratio. Surrogate factors should be qualified and further validated in multiple clinical trials, and this validation should ideally occur using a variety of treatment types to establish that the surrogate factor is reliable independent of treatment. Examples of potential surrogate markers for survival in mCRPC may include a drop in prostate-specific antigen level (PSA) or circulating tumor cell (CTC) count over time, an improvement in pain or quality of life, tumor shrinkage and progression-free survival, or the disappearance of bone lesions. A surrogate biomarker such as PSA response or progression may work for certain classes of drugs such as hormonal therapies or cytotoxic therapies (ie, abiraterone acetate or MDV3100) but may not work well for other types of drugs, such as immunotherapies or targeted cytostatic agents (ie, sipuleucel-T or tasquinimod). For example, the survival benefit of sipuleucel-T may be mediated through more subtle delays in tumor growth that are not well appreciated in the first few months following therapy using traditional Response Evaluation Criteria In Solid Tumors (RECIST) metrics. Thus, surrogate markers must be interpreted in the context of a drug's mechanism of action.

For a biomarker to qualify as a surrogate factor, it must first meet the criteria established by the Oncology Biomarker Qualification Initiative, a collaboration between the US Food and Drug Administration (FDA), the National Cancer Institute, and the Centers for Medicare and Medicaid Services.[10] This initiative assists in the development, evaluation, and validation of biomarkers—including surrogate factors—and serves to guide both industry and academia regarding the establishment of biomarkers in the clinic. Successful assessment of a biomarker requires a positive evaluation in multiple phase III clinical trials; thus, it is a rigorous process that must be developed concurrently, and eventually prospectively, with drug development. The introduction of a biomarker into the clinical setting is a lengthy process; nonetheless, surrogate biomarkers have great potential. To date, no surrogate factors have been validated in mCRPC. However, much research is devoted to this area, and some leads are beginning to emerge, several of which are described below.

Changes in the Prostate-Specific Antigen Level

PSA has long been used in the interpretation of benefit in the therapy of prostate cancer, including following local therapies, androgen deprivation, and even with chemotherapy. Two key papers have investigated the association between PSA declines and survival in men with docetaxel-treated mCRPC.[11,12] Both articles specifically focused on the use of PSA decline as a surrogate marker. Because of the discrepancy between these 2 studies, however, PSA declines alone do not appear to be sufficient for making treatment decisions or approval recommendations.

In 2006, retrospective data from the SWOG (Southwest Oncology Group) 99-16 randomized study were used to evaluate PSA decline as a surrogate marker for overall survival (OS).[11] In SWOG 99-16, mCRPC patients were randomly assigned to treatment with either docetaxel plus estramustine or mitoxantrone plus prednisone. In this large phase III trial of over 700 men, several measures of PSA decline following treatment initiation were strongly associated with survival. These measures included 3-month PSA declines of 20–40%, 2-month PSA declines of 30%, and PSA velocity at 2 months and 3 months. The proportion of treatment effect explained by a PSA decline greater than or equal to 30% was 1.0, indicating strong surrogacy in this trial. Although PSA declines greater than or equal to 50% are commonly included in clinical trial analyses, this endpoint did not meet any criteria for surrogacy. Thus, PSA declines in this trial were found to be strongly associated with survival, but surrogacy across trials was not established.

A 2007 analysis of the TAX 327 randomized trial also examined various degrees of PSA decline as a surrogate marker for OS.[12] In TAX 327, men with mCRPC were treated with either docetaxel (using 1 of 2 schedules) or mitoxantrone; both drugs were administered with prednisone. PSA data collected at baseline and at 3 months were available for 989 patients. The highest degree of surrogacy was associated with a decline in PSA level of at least 30% within 3 months of initiating treatment; this endpoint accounted for 66% of the observed treatment effect and, after adjusting for treatment effect, was associated with a hazard ratio (HR) for OS of 0.50 (95% confidence interval [CI], 0.43–0.58). While this endpoint (PSA decline ≥30%) met surrogacy criteria in this trial, the level of surrogacy was modest (two thirds of the benefit of docetaxel was explained by this degree of PSA decline); this finding combined with the fact that weekly docetaxel had a similar proportionate PSA decline without a similar survival benefit led many to reject PSA changes alone as a surrogate biomarker of survival.

Progression-Free Survival

Progression-free survival (PFS), measured by radiographic, symptomatic, or PSA changes over time, is particularly difficult to judge in mCRPC patients because the majority of these men have bone-only distant disease. Thus, traditional measures of PFS, such as RECIST, do not apply well to this disease. For example, bone scan flares, or healing reactions, are known to commonly occur with effective systemic therapies such as abiraterone, and should not necessarily be reason alone to stop therapy; these flares, however, may result in confusion around progression determinations and the premature cessation of therapy.[13] In 2008, the Prostate Cancer Clinical Trials Working Group (PCWG2) released recommendations for considering clinical trial endpoints in men with mCRPC that reflect these considerations.[14]

One of the key recommendations in this publication was that confirmatory bone scans should be used to help

account for the presence of bone scan flare. For example, if a man with a PSA level of 200 ng/mL initiates treatment with a systemic agent such as abiraterone acetate or docetaxel, he may show an apparent new lesion on his first bone scan assessment despite a substantial drop in PSA level and pain improvements. This new lesion is likely to represent a flare, or healing reaction, in response to treatment, but it is often misclassified as progression. To overcome this issue, the PCWG2 established the idea of performing confirmatory bone scans and requiring the observation of additional new lesions over time to document radiographic progression before stopping therapy.

The use of PFS as a surrogate marker for OS depends on the mechanism of action of the drug in question, especially for the most recently approved agents. With cytotoxic therapies such as docetaxel and cabazitaxel, the relationship between PFS and OS is approximately linear, as it is for hormonal therapies such as abiraterone. This means that the improvements in PFS are also generally reflected in the same relative improvements in OS in these studies. However, improvements in PFS may be delayed or not apparent with immunotherapies such as sipuleucel-T, which tend to take a prolonged period of time to elicit a response. This has led to revised guidelines around defining progression in trials of immunotherapies for cancer.[15] In CRPC, antiangiogenic therapies such as bevacizumab may result in initial improvements in PFS without survival benefits for a variety of reasons, as has been observed in CALGB 90401 (a phase III trial of docetaxel with or without bevacizumab).[16] Finally, hormonal therapies, such as abiraterone and MDV3100, will likely have a strong impact on PSA levels prior to impacting survival. However, the surrogate relationship of PFS with OS in these trials has not yet been established using our newer criteria. Thus, much work needs to be done through a series of positive randomized studies to demonstrate that PFS can act as a reliable surrogate. Heading into 2012, we are fortunate to have had many new active agents and positive clinical trials that should be able to address these questions going forward.

Circulating Tumor Cells

Circulating tumor cells (CTCs) are cells that originate from the primary tumor or metastatic sites and are present in the blood. Currently, only 1 CTC assay has been cleared by the FDA (CellSearch); this assay uses an epithelial cell adhesion molecule–targeting enrichment method to capture CTCs from the blood, after which a nucleated cell is ruled to be a CTC based on 3 factors: size, expression of a cytokeratin marker, and lack of a specific leukocyte marker. In prostate cancer, a threshold of at least 5 CTCs per 7.5 mL of blood is considered to be indicative of unfavorable prognosis. FDA clearance of this assay was primarily based on a study that showed that the number of CTCs at baseline was prognostic among men with mCRPC who were initiating a new line of chemotherapy.[17] After therapy was started, the number of CTCs was found to also be highly associated with survival.

Multiple phase III clinical trials are currently investigating CTC level or changes as a surrogate endpoint. In a study presented at the 2011 American Society of Clinical Oncology Annual Meeting, Scher and colleagues reported that CTCs were significantly associated with OS following abiraterone treatment in mCRPC patients.[18] As part of a planned final analysis of the phase III COU-AA-301 trial, the number of CTCs was evaluated as a viable surrogate marker for OS. Patients with an unfavorable CTC level at baseline who were randomized to the abiraterone acetate arm achieved significantly higher rates of conversion to favorable CTC levels compared to patients who were randomized to the placebo arm (48% vs 17% at Week 12; $P<.0001$). CTC conversion from unfavorable to favorable levels was significantly associated with OS. Thus, in this trial, a biomarker profile including CTCs was highly associated with survival outcomes with abiraterone acetate; however, whether CTC changes alone have surrogate value across multiple trials and can inform treatment decisions awaits further study. CTCs as currently defined are being evaluated in multiple phase III studies currently as surrogates of OS in men with mCRPC. In addition, other methods of measuring CTCs and alternative CTC phenotypes that lack epithelial markers are under evaluation and are worthy of study in the context of therapeutic decision-making and surrogacy.[19,20]

Improvements in Pain and Quality of Life

A number of patient-reported outcomes have been described in mCRPC; some of these endpoints have led to the approval of therapeutic agents. For example, a significant improvement in patient-reported pain led to the approval of mitoxantrone as a treatment for mCRPC.[21] Other patient-reported outcomes that have been evaluated in clinical trials of men with mCRPC include quality of life. Finally, not all endpoints need be OS; other measures of direct patient benefit, such as pain palliation and the prevention or delay of skeletal-related events (as used in the approvals of zoledronic acid and denosumab), are important themselves.

In addition to their importance in the approval of new therapies, patient-reported outcomes may also have potential as surrogate factors. Several reports have shown that improvement in pain is highly associated with patient survival. For example, of the 466 patients enrolled in the TAX 327 trial who had significant pain at baseline, 29% experienced a pain response that was prognostic independent of treatment effect.[12] In this study, pain was found to be a modest surrogate for survival, with an estimated proportion of treatment effect of 0.64, indicating a moderate surrogate association. However, a drawback to using these endpoints in this manner is that they must be collected in a validated and reproducible manner that is objectively quan-

tifiable, and symptoms must be recorded using a rigorous collection process that accounts for patient and treatment variables such as the use of narcotic analgesia. Ongoing phase III trials of agents such as XL184 and their effect on patient-reported outcomes are important steps to linking these outcomes to survival and direct clinical benefit.

Conclusion

Many biomarkers are available to oncologists to help them make critical decisions in the clinic about continuing or stopping a systemic therapy, including blood tests, radiographic changes, and patient-reported outcomes. The use of these biomarkers in mCRPC is context-dependent.[22] Many biomarkers have prognostic value and can help to inform a patient about his outcome over time. In contrast, while many biomarkers potentially have predictive benefit, none have yet been validated to inform on specific therapies in this disease. Unlike KRAS mutations in colorectal cancer and BRAF mutations in melanoma, we do not yet have predictive biomarkers in men with mCRPC that are tied directly to a specific targeted therapy. One exception to this statement could be the presence of significant pain as a predictor for lack of benefit with sipuleucel-T, given the delayed onset of this immunotherapy and the eligibility criteria for the study. Potential predictive biomarkers in CRPC are discussed elsewhere but may include tumor mutational status (such as PTEN loss or androgen receptor mutations), circulating androgen levels, and other circulating biomarkers such as VEGF levels.[22] Likewise, the presence of bone metastases is likely predictive for benefit with zoledronic acid or denosumab, which largely work within the bone microenvironment. However, these factors have not yet been rigorously studied as true predictive biomarkers to date. Surrogate biomarkers may help to limit toxic therapy, risk stratify patients so that they can receive therapies that will provide maximum benefit with minimal harm, and also help to identify active drugs early in the course of treatment. To date, no biomarker has qualified as a surrogate for OS in mCRPC; thus, OS remains the preferred endpoint for drug development in this disease at this time. Of the surrogate biomarkers under evaluation, CTCs are furthest along in development and validation. Qualification of predictive and surrogate biomarkers requires a long-term investment across multiple prospective trials. However, this effort could yield significant benefits, as these biomarkers have the potential to maximize effective therapies in those populations that are most likely to have a positive response, while minimizing harm, cost, and toxicity.

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References

1. National Comprehensive Cancer Network. Prostate cancer. NCCN Clinical Practice Guidelines in Oncology. Version 4.2011. http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed November 1, 2011.
2. Ross PL, Gerigk C, Gonen M, et al. Comparisons of nomograms and urologists' predictions in prostate cancer. *Semin Urol Oncol*. 2002;20:82-88.
3. Touijer K, Scardino PT. Nomograms for staging, prognosis, and predicting treatment outcomes. *Cancer*. 2009;115(13 suppl):3107-3111.
4. Shariat SF, Karakiewicz PI, Roehrborn CG, Kattan MW. An updated catalog of prostate cancer predictive tools. *Cancer*. 2008;113:3075-3099.
5. Halabi S, Small EJ, Kantoff PW, et al. Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. *J Clin Oncol*. 2003;21:1232-1237.
6. Armstrong AJ, Garrett-Mayer ES, Yang YC, de Wit R, Tannock IF, Eisenberger M. A contemporary prognostic nomogram for men with hormone-refractory metastatic prostate cancer: a TAX327 study analysis. *Clin Cancer Res*. 2007;13:6396-6403.
7. Smaletz O, Scher HI, Small EJ, et al. Nomogram for overall survival of patients with progressive metastatic prostate cancer after castration. *J Clin Oncol*. 2002;20:3972-3982.
8. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. *Stat Med*. 1989;8:431-440.
9. Buyse M, Molenberghs G, Burzykowski T, Renard D, Geys H. The validation of surrogate endpoints in meta-analyses of randomized experiments. *Biostatistics*. 2000;1:49-67.
10. Barker AD. Oncology Biomarker Qualification Initiative: NCI-FDA-CMS collaboration to speed development of cancer therapies. National Cancer Advisory Board Meeting. June 14, 2006. http://deainfo.nci.nih.gov/advisory/ncab/138_0606/presentations/BarkerOBQI.pdf. Accessed November 1, 2011.
11. Petrylak DP, Ankerst DP, Jiang CS, et al. Evaluation of prostate-specific antigen declines for surrogacy in patients treated on SWOG 99-16. *J Natl Cancer Inst*. 2006;98:516-521.
12. Armstrong AJ, Garrett-Mayer E, Ou Yang YC, et al. Prostate-specific antigen and pain surrogacy analysis in metastatic hormone-refractory prostate cancer. *J Clin Oncol*. 2007;25:3965-3970.
13. Ryan CJ, Shah S, Efstathiou E, et al. Phase II study of abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer displaying bone flare discordant with serologic response. *Clin Cancer Res*. 2011;17:4854-4861.
14. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol*. 2008;26:1148-1159.
15. Hoos A, Eggermont AM, Janetzki S, et al. Improved endpoints for cancer immunotherapy trials. *J Natl Cancer Inst*. 2010;102:1388-1397.
16. Kelly WK, Halabi S, Carducci MA, et al. A randomized, double-blind, placebo-controlled phase III trial comparing docetaxel, prednisone, and placebo with docetaxel, prednisone, and bevacizumab in men with metastatic castration-resistant prostate cancer (mCRPC): survival results of CALGB 90401. 2010 Annual Meeting of the American Society of Clinical Oncology; June 4–8, 2010; Chicago, Illinois. Abstract LBA4511.
17. de Bono JS, Scher HI, Montgomery RB, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin Cancer Res*. 2008;14:6302-6309. Erratum in: *Clin Cancer Res*. 2009;15:1506.
18. Scher HI, Heller G, Molina A, et al. Evaluation of circulating tumor cell (CTCs) enumeration as an efficacy response biomarker of overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC): planned final analysis (FA) of COU-AA-301, a randomized, double-blind, placebo-controlled, phase III study of abiraterone acetate (AA) plus low-dose prednisone (P) post docetaxel. 2011 Annual Meeting of the American Society of Clinical Oncology; June 3–7, 2011; Chicago, Illinois. Abstract LBA4517.
19. Danila DC, Fleisher M, Scher HI. Circulating tumor cells as biomarkers in prostate cancer. *Clin Cancer Res*. 2011;17:3903-3912.
20. Armstrong AJ, Marengo MS, Oltean S, et al. Circulating tumor cells from patients with advanced prostate and breast cancer display both epithelial and mesenchymal markers. *Mol Cancer Res*. 2011;9:997-1007.
21. Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol*. 1996;14:1756-1764.
22. Armstrong AJ, Eisenberger MA, Halabi S, et al. Biomarkers in the management and treatment of men with metastatic castration-resistant prostate cancer. *Eur Urol*. 2011 Nov 12. Epub ahead of print.

Immune System Activation and Immunotherapy in Metastatic Castration-Resistant Prostate Cancer

Anna C. Ferrari, MD

A cancer vaccine is an active form of immunotherapy that utilizes live cells, whole cells, viral vectors, DNA, or peptides that are aimed at inducing an effective and long-lasting immune response against a specific tumor-associated antigen. Because the target of this therapy is the immune system, cancer vaccines are not directly cytotoxic to tumor cells or normal cells, and they have a low toxicity profile. The antitumor effect of the adaptive immune response is achieved through a balance of a complex network of various cellular subsets of effectors and suppressor T cells, myeloid cells, and macrophages; the production of specific antibodies to tumor antigens; and secretion of stimulatory and inhibitory cytokines that augment or inhibit the T-cell response at the tumor sites.[1] Humanized monoclonal antibodies are designed to directly target and block the activity of a specific molecule in a tumor cell or an immune cell. Unlike cancer vaccines, humanized monoclonal antibodies are passive forms of immunotherapy, as they do not stimulate the host immune response and require repeated administration to sustain efficacy. Several immunotherapies are under clinical evaluation or currently in use in mCRPC patients.

Sipuleucel-T is an autologous dendritic cell vaccine produced by loading the patient's circulating mononuclear cells ex vivo with a fusion protein (PA2024) comprised of the prostatic acid phosphatase (PAP) that is expressed in prostate cancer cells and granulocyte-macrophage colony-stimulating factor (GM-CSF) to stimulate the dendritic cell response.[2] In a double-blind, placebo-controlled, phase III trial in minimally symptomatic or asymptomatic mCRPC patients (the IMmunotherapy Prostate AdenoCarcinoma Treatment [IMPACT] study), sipuleucel-T induced a 22.5% relative reduction in the risk of death (HR, 0.775; 95% CI, 0.61–0.98; *P*=.03) and a 4.1-month improvement in median OS (25.8 months vs 21.7 months) compared to placebo. These results led to FDA approval, although no advantage in median time to objective disease progression was observed. Grade 3–4 toxicity was low (6.8%) and consisted primarily of fatigue, chills, and back pain.[3]

PROSTVAC-VF is an antigen-specific, viral vector–based vaccine that uses the Vaccinia and fowlpox viruses to carry a modified PSA gene and 3 co-immunostimulatory molecules (TRICOM). The Vaccinia recombinant is used to "prime" and the fowlpox recombinant is used to "boost" the immune response. In randomized phase II studies, PROSTVAC-VF–treated patients had a significant increase in OS compared to placebo-treated patients; PROSTVAC-VF is currently in phase III clinical trials.[4] TroVax is also an antigen-specific, viral-based vaccine that uses the poxvirus MVA to deliver the tumor antigen 5T4, which is expressed in many solid tumors, including metastatic prostate cancer. A single-arm, phase II study of TroVax administered with or without GM-CSF in 27 subjects with mCRPC showed that subjects with 5T4-specific cellular responses had a significant increase in time to disease progression.[5] A randomized phase II study in combination with docetaxel is in progress.

In contrast, GVAX is a heterologous whole tumor cell vaccine made using LNCaP and PC3 prostate tumor cell lines engineered to express GM-CSF; the aim of this vaccine is to expose the patient to multiple prostate cancer antigens. However, studies with the GVAX vaccine have been discontinued.[6]

Ipilimumab is a humanized monoclonal antibody directed against activated cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), which is a surface receptor that mediates T-cell tolerance to self antigens. As a result of this block, treatment with ipilimumab induces nonspecific immune stimulation with increased circulating CD8+ cells and autoimmune reactions. A phase I trial of ipilimumab has been completed, and a phase III trial is enrolling patients.[7]

Approval of sipuleucel-T established a new frontier in cancer therapeutics for solid tumors by proving the concept that stimulation of the immune system can have profound indirect antitumor effects that translate to significant change in disease progression, even among patients with life expectancies of only 24–30 months. More specifically, in mCRPC patients, sipuleucel-T has provided a new life-extending treatment option with several unique features. First, unlike hormone treatment and chemotherapy, sipuleucel-T has a very low toxicity profile; thus, it does not compromise quality of life or aggravate medical comorbidities that are common in patients with advanced prostate cancer. Second, its unique mechanism of action does not generate overlapping toxicity with other effective treatment modalities that can be subsequently delivered safely, as was the case in the subgroup of patients who received chemotherapy or additional hormones at progression after vaccination in the IMPACT trial. Third, because activation of the immune system by sipuleucel-T persists for several months, the antitumor response to agents that directly target tumor cells may be enhanced by a more robust host immune response to damaged prostate cancer cells. However, the optimum sequencing and timing of

sipuleucel-T with other agents is unknown and needs to be tested in clinical trials.

Another unique feature of sipuleucel-T, as well as PROSTVAC-VF, is that the therapeutic benefit (such as an increase in OS) is achieved even in the absence of tumor regression and with no difference in the median time to objective disease progression as measured by RECIST, bone scans, and PSA level.[8,9] This finding is important, as PFS has traditionally been correlated with OS and has commonly been used as a surrogate endpoint for evaluating drug activity and making decisions regarding the treatment of mCRPC. However, given the mechanism of action of vaccines, it is not surprising that these markers were not very useful. Both RECIST and bone scan criteria rely on measurement of tumor size and assume that an active agent induces tumor shrinkage within a relatively short period of time. For traditional treatments such as systemic cytotoxic chemotherapy, this assumption is applicable, as cytotoxic chemotherapy and hormonal drugs directly target the tumor cells' proliferative and cell survival machinery. However, the principles of chemotherapy do not apply to adaptive immunotherapy, which instead targets tumors indirectly, following adequate and specific stimulation of the tiered and complex multistep immune system. Thus, while there is an immediate immune inflammatory response to vaccination, the most effective long-term antitumor immune response is slow to develop, and the proliferative properties of the tumor are not immediately blocked.[10] As a result, the tumor continues to grow, and the acute immune inflammatory response may actually enlarge the radiologic appearance of metastasis and/or cause the development of new visible foci.[11]

Despite the slow immune response to vaccination and the lack of a direct effect on the tumor itself, vaccination with sipuleucel-T can prolong OS, suggesting that a change in the growth dynamics of the tumor may have occurred beyond the standards of PFS, and these changes were not captured or were confounded by the use of other therapies.[12] Given the opposing dynamics between a slow immune response after vaccination and unchecked tumor growth, patients with slowly growing tumors and a relatively long life expectancy are likely to benefit even more than advanced disease patients from these therapies. Therefore, identifying and validating biomarkers of response and outcomes will be essential to accelerate the development of these approaches.[13]

Biomarkers for Treatment and Response

Currently, all drugs approved by the FDA (including vaccines) must show a clinical benefit in terms of endpoints such as an improvement in symptoms, function, or survival. However, this requirement slows both the evaluation of new agents and the management of patients in clinical practice. As demonstrated by the sipuleucel-T and PROSTVAC trials, endpoints that have traditionally been used to evaluate the effect of new prostate cancer drugs—such as RECIST, bone scans, PSA levels, and quality of life—have not been useful predictors of outcome. More recently, enumeration of CTCs has been approved by the FDA as a method for monitoring mCRPC progression and prognosis.[14] However, the value of CTCs as a marker of response and a surrogate for outcomes has yet to be confirmed in prospective randomized trials.[15] Further, clinicians and researchers lack experience in using CTCs in the context of vaccines (although the use of CTCs in conjunction with ipilimumab has been tested).

An alternative to direct tumor measurements is to develop biomarkers of immune response to assess the activity of immunotherapy and to test their predictive value in prospective immunotherapy clinical trials.

Biomarkers are important for aiding in selection of drugs and combination regimens that might be more effective for patients with advanced disease, including which agent should be used and when it should be administered to avoid negatively interfering with the efficacy of the immunotherapy. These decisions are very important, given that clinicians now have several new agents at their disposal; however, little is known about their optimal timing and sequencing with immunotherapy. Moreover, some of these agents require concomitant use of steroids, which may suppress the immune system and negate the effect of immunotherapy. Biomarkers will also be critical to introduce tumor vaccines in patients with earlier stages of the disease.

However, the development and validation of biomarkers for immunotherapy poses a significant methodological challenge. Further, the establishment of validated biomarkers is a lengthy process that requires careful evaluation of the mechanism of action of the agent for which the biomarker will be utilized, extensive technical validation of the assays with performance under standardized protocols, and consistent testing in large prospective clinical trials. Fortunately, a number of assays and methods are available to measure several different components of the immune response.[16]

To address the issue of immune-monitoring assays and to determine their ability to measure response, a panel of experts developed a series of guidelines for performing immune monitoring using reproducible and technically validated protocols.[17] These guidelines established threshold values of response; they also established the need to perform repeated testing in order to collect reliable response data that can be used to test the efficacy of immunotherapies and prospectively assess their value as surrogate endpoints of clinical outcome. This panel recommended performing at least 2 basic cellular response assays, such as enzyme-linked immunosorbent response spot (ELISPOT) assays and intracellular cytokine staining or flow cytometry with total and subcategory lymphocyte count. Assays available to measure antigen-specific cellular responses include major histocompatibility complex–peptide tetramer staining, T-cell

proliferation assays, cytotoxicity assays, and delayed-type hypersensitivity testing, as well as induction of antigen-specific antibody responses by enzyme-linked immunosorbent assay (ELISA) and measurement of immune cytokine secretion in patients' serum.

Immune monitoring is helping to elucidate the mechanism of activity and duration of response to vaccination with sipuleucel-T. Immune monitoring of Lot release CD54 upregulation and in vivo studies of humoral and cellular proliferation responses at baseline and at Weeks 6, 14, and 26 were measured in treated and control patients in the IMPACT study and repeated at Weeks 0 and 6 in the Open-Label Active Cellular ImmunoTherapy phase II trial. Results of these studies indicated that sipuleucel-T activates the immune system via a prime-boost mechanism and that, starting at Week 6, there is a significant increase in memory T cells and T-cell proliferation associated with a robust humoral antibody response to both PA2024 and PAP that remains significant at 6 months (Week 26).[18-20]

Preliminary evidence also suggests that monitoring immune response may be predictive. In the IMPACT study, antibody titers above 1/400 dilution against PA2024 by ELISA were significantly higher in the sipuleucel-T–treated group and were associated with improved OS.[3,18,19] In the PROSTVAC study, ELISPOT was performed in 32 chemotherapy-naïve patients who were treated with vaccine. Patients with a 6-fold greater ELISPOT response after vaccination trended towards improved survival compared to those with a lower result.[21]

Conclusion

The approval of sipuleucel-T was a major achievement, as it proved that autologous immunotherapy with an antigen-targeted cancer vaccine can effectively stimulate an adaptive immune response. As a result of such therapy, the dynamics of mCRPC have been favorably altered, and patients can experience prolonged OS with minimal toxicity. The approval of sipuleucel-T also demonstrated that current standards for evaluating treatment response, such as RECIST, bone scans, and PSA levels—which are used to measure PFS—are unable to predict outcomes following immunotherapy. Given the uncoupling between OS and these standard surrogates, identifying and testing novel immune biomarkers of response is now imperative. Establishment of these biomarkers will necessitate a consensus among investigators regarding a standardized set of assays to quantify and characterize immune responses and the correlation of these measurements with OS in the context of well-designed clinical trials. Yet another challenge may arise in interpreting the results of both immune and standard biomarkers of response in combination trials of vaccines with cytotoxic chemotherapy and hormone therapy.

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References

1. Cha E, Fong L. Immunotherapy for prostate cancer: biology and therapeutic approaches. *J Clin Oncol*. 2011;29:3677-3685.
2. Higano CS, Small EJ, Schellhammer P, et al. Sipuleucel-T. *Nat Rev Drug Discov*. 2010;9:513-514.
3. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363:411-422.
4. Kantoff PW, Schuetz TJ, Blumenstein BA, et al. Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2010;28:1099-1105.
5. Amato RJ, Drury N, Naylor S, et al. Vaccination of prostate cancer patients with modified vaccinia ankara delivering the tumor antigen 5T4 (TroVax): a phase 2 trial. *J Immunother*. 2008;31:577-585.
6. Higano CS, Corman JM, Smith DC, et al. Phase 1/2 dose-escalation study of a GM-CSF-secreting, allogeneic, cellular immunotherapy for metastatic hormone-refractory prostate cancer. *Cancer*. 2008;113:975-984.
7. Fong L, Kwek SS, O'Brien S, et al. Potentiating endogenous antitumor immunity to prostate cancer through combination immunotherapy with CTLA4 blockade and GM-CSF. *Cancer Res*. 2009;69:609-615.
8. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst*. 2000;92:205-216.
9. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the prostate cancer clinical trials working group. *J Clin Oncol*. 2008;26:1148-1159.
10. Madan RA, Gulley JL, Fojo T, Dahut WL. Therapeutic cancer vaccines in prostate cancer: the paradox of improved survival without changes in time to progression. *Oncologist*. 2010;15:969-975.
11. Ribas A, Chmielowski B, Glaspy JA. Do we need a different set of response assessment criteria for tumor immunotherapy? *Clin Cancer Res*. 2009;15:7116-7118.
12. Gulley JL, Drake CG. Immunotherapy for prostate cancer: recent advances, lessons learned, and areas for further research. *Clin Cancer Res*. 2011;17:3884-3891.
13. Hales RK, Banchereau J, Ribas A, et al. Assessing oncologic benefit in clinical trials of immunotherapy agents. *Ann Oncol*. 2010;21:1944-1951.
14. Danila DC, Heller G, Gignac GA, et al. Circulating tumor cell number and prognosis in progressive castration-resistant prostate cancer. *Clin Cancer Res*. 2007;13:7053-7058.
15. Danila DC, Morris MJ, de Bono JS, et al. Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated castration-resistant prostate cancer. *J Clin Oncol*. 2010;28:1496-1501.
16. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15:7412-7420.
17. Hoos A, Eggermont AM, Janetzki S, et al. Improved endpoints for cancer immunotherapy trials. *J Natl Cancer Inst*. 2010;102:1388-1397.
18. Stewart FP, dela Rosa CP, Sheikh NA, et al. Correlation between product parameters and overall survival in three trials of sipuleucel-T, an autologous active cellular immunotherapy for the treatment of prostate cancer. *J Clin Oncol*. 2010; 28(suppl):4552.
19. Sims RB, Lin LRC, dela Rosa CP, Sheikh NA, Whitmore JB, Frohlich MW. Elevated eosinophils following treatment with sipuleucel-T in men with prostate cancer is associated with antigen-specific immune response and prolonged survival. 52nd American Society of Hemotology Annual Meeting and Exposition; December 4, 2010; Orlando, Florida. Abstract 1491.
20. Petrylak D, Corman J, Hall S, et al. Cellular and humoral immune system activation by sipuleucel-T: preliminary data from the OpenACT phase II trial. 2011 Société Internationale d'Urologie Meeting; October 15–16, 2011; Berlin, Germany. Abstract MP-16.01.
21. Muir G, Rajbabu K, Callen C, Fabre JW. Preliminary evidence that the allogeneic response might trigger antitumour immunity in patients with advanced prostate cancer. *BJU Int*. 2006;98:989-995.

Role of Biomarkers in Risk Stratifying, Assessing, and Selecting Systemic Therapies

David I. Quinn, MD

When considering prognostic and predictive biomarkers for mCRPC, clinicians should note that a set of prognostic biomarkers have been validated for use in the very early stages of prostate cancer diagnosis and treatment of localized disease. Chief among these biomarkers are serum PSA level, disease stage, and Gleason score. Prior to the initiation of localized therapy (generally radiation, surgery, or watchful waiting), the velocity at which the PSA level rises, referred to as PSA doubling time, can also be predictive. As the disease progresses and evolves into metastatic castration-resistant cancer, these conventional biomarkers generally have less value, although some factors are still important. For example, historical evidence shows that, among all patients with castration-resistant disease, those who have no evidence of metastatic disease (M0) have a clearly improved prognosis compared to patients with metastases.

Prognostic Biomarkers

A prognostic biomarker is a disease or host characteristic that predicts the natural history of a particular disease (usually OS or disease-free survival). In mCRPC, several prognostic factors are important. For example, historical data suggest that the distribution of metastases has an important effect on outcomes. Specifically, patients with visceral metastases involving the liver, spleen, or brain often have worse outcomes than patients with only lymph node or bone metastases; patients with pulmonary metastases have an intermediate prognosis. These trends are currently being validated in prospective clinical trials. Unfortunately, these stratifications may not have substantive value from a clinical standpoint, due to the lack of treatments that are specifically predicated by metastatic distribution.

Kinetic PSA biomarkers and imaging studies are more widely used in mCRPC. These imaging methods may include conventional bone scans combined with computed tomography (CT) scans of the abdomen and pelvis, or magnetic resonance imaging (MRI) scans that provide cross-sectional imaging of the abdomen and pelvis with variable imaging of the chest. However, questions arise as to how useful these biomarkers are and how they might be used in the management of mCRPC.

In mCRPC, PSA level and PSA doubling time currently remain the primary serum markers for assessing disease response and progression. Evidence supporting the use of PSA level in this setting is variable; in general, this evidence is based on extrapolation from earlier disease stages. For example, in 2006, Hussain and colleagues assessed patients from the SWOG 9346 (INT-0162) trial and found that, when a hormone-naïve prostate cancer patient with metastatic disease initiates androgen-deprivation therapy, achievement of a PSA value of 4 ng/mL or lower after 7 months of therapy is a strong predictor of survival.[1,2] Compared to patients with a PSA level above 4 ng/mL, patients with a PSA level greater than 0.2 ng/mL but less than or equal to 4 ng/mL had less than one-third the risk of death. The median OS for patients with PSA levels above 4 ng/mL, between 0.2 ng/mL and 4 ng/mL, and 0.2 ng/mL or lower following 7 months of androgen-deprivation therapy was 13 months, 44 months, and 75 months, respectively. These results have been confirmed in 3 other studies.[3-5] These results suggest that PSA level is an important prognostic factor that allows for risk stratification of patients. Importantly, this finding allows clinicians to select patients whose PSA level does not fall to 4 ng/mL or below and identify them as castration-resistant. Inevitably, these patients are going to progress relatively quickly to castration-resistant disease.

Other reports have analyzed the prognostic ability of PSA level in mCRPC patients treated with chemotherapy; specifically, studies have evaluated the patient populations from the SWOG 99-16 and TAX 327 trials. Both 2004 studies compared differing schedules of docetaxel with mitoxantrone, which was the standard-of-care treatment at that time.[6-8] Subsequent post-hoc analyses of these studies demonstrated that a fall in PSA level, measured in various ways (30% reduction from baseline, 50% reduction from baseline, etc), can effectively predict OS.[9-11] However, the value of PSA level as a surrogate marker for OS was not sufficient in these studies, which has prevented the adoption of PSA decline as an outcome measure that can be used alone in clinical trials instead of waiting for effects on OS. Interestingly, the use of PSA kinetics as a biomarker in patients with mCRPC is most unreliable during the first 12 weeks of chemotherapy, as major variation may occur during the first 4 cycles of treatment.

Other post-hoc studies of the SWOG 99-16 and TAX 327 trials have evaluated the use of response-based criteria, such as RECIST, for analyzing CT images and bone scans. However, these imaging studies are somewhat limited in prostate cancer, as the majority of patients have dominant disease burden in the bone and, therefore, are not well evaluated by RECIST. Determining treatment response is very difficult when evaluating bone lesions, as all bone disease must be eradicated in order to effectively judge a response. Like positron emission tomography (PET) imaging, CT and MRI scanning are limited in mCRPC because the majority of patients have lymph node disease. Lymph node disease within the pelvis is especially difficult to measure consistently, even for skilled clinicians and radiologists. However, evaluation using RECIST can be effective when measurements from lymph nodes and other visceral metastases are used.

In these cases, data from the SWOG 99-16 and TAX 327 trials show that patients who show a response according to RECIST have better survival than patients whose best response is stable disease or progressive disease.[12]

Several studies are now testing whether progression observed on bone scans, as demonstrated by the presence of a new bone lesion, can be used as a prognostic biomarker. An important consideration is that the appearance of a new bone lesion on a bone scan may actually be a bone flare, which is indicative of a positive response to new therapy. Many new study protocols are currently requiring confirmation with a second bone scan 6–12 weeks after the first scan, in order to confirm new spots, before making a diagnosis of disease progression.

A new bone scan method, based on sodium fluoride PET scanning, has recently been tested and appears to be more sensitive in mCRPC.[13] This novel method is not only more sensitive for detecting new lesions in patients but also has the potential to better detect a variation in response to therapy. Currently, this method is under investigation in a large registry of Medicare-insured patients in the United States.

Several other prognostic biomarkers have also been investigated in mCRPC. These include baseline levels of serum factors such as lactate dehydrogenase, hemoglobin, alkaline phosphatase, and N-telopeptide. Inflammatory and hematologic markers include C-reactive protein, interleukin (IL)-6, IL-8, and D dimers. As already discussed, CTCs have prognostic value in mCRPC. In a prospective series of patients who were treated with chemotherapy, de Bono and colleagues found that higher CTC counts (≥5 cells per 7.5 mL blood) were associated with a poorer OS prognosis.[14] This study also showed that, after a few cycles of chemotherapy, patients could potentially be converted from an unfavorable risk group to a favorable risk group, based on their CTC count. Further prospective studies on the use of CTCs in mCRPC are needed to assess the full potential value of this biomarker.

Predictive Biomarkers

Predictive biomarkers provide information about whether a patient will respond to a particular therapeutic intervention. No predictive biomarkers have been validated in mCRPC. One intriguing possibility is the use of CTCs as a predictive biomarker; in this case, enumeration of these cells may not be as important as their particular molecular characteristics. Sensitivity markers in the CTCs may portend treatment response to cabazitaxel; for example, mutations in β-tubulin, the main target of this compound, may predict that patients will not benefit from this particular therapy. This knowledge could allow clinicians to select a better alternative therapy for the patient. Alternatively, a preliminary evaluation has been performed to determine whether there are any regulatory genes that predict outcome to hormonal therapy. In the future, CTCs could be analyzed to look for these genetic markers predictive of response to particular agents.

Predictive biomarkers will be especially valuable as novel agents are evaluated in mCRPC. For example, changes in the level of clusterin, a target of OGX011, may help to select patients for this therapy. Also, researchers have observed that certain mutations in the androgen receptor can trigger growth factor signaling. These growth factor pathways may become dominant in mCRPC, possibly allowing them to bypass conventional androgen-receptor signaling pathways.

Conclusion

The use of biomarkers to risk stratify mCRPC patients and select treatments holds great potential. Although current biomarkers are limited to PSA level, PSA doubling time, bone scans, and RECIST, many novel biomarkers are under investigation. The use of biomarkers is becoming increasingly important, as the number of therapies available for mCRPC has multiplied, providing patients with several effective options.

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References

1. Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). *J Clin Oncol*. 2006;24:3984-3990.
2. Hussain M, Goldman B, Tangen C, et al. Prostate-specific antigen progression predicts overall survival in patients with metastatic prostate cancer: data from Southwest Oncology Group Trials 9346 (Intergroup Study 0162) and 9916. *J Clin Oncol*. 2009;27:2450-2456.
3. Choueiri TK, Xie W, D'Amico AV, et al. Time to prostate-specific antigen nadir independently predicts overall survival in patients who have metastatic hormone-sensitive prostate cancer treated with androgen-deprivation therapy. *Cancer*. 2009;115:981-987.
4. Sasaki T, Onishi T, Hoshina A. Nadir PSA level and time to PSA nadir following primary androgen deprivation therapy are the early survival predictors for prostate cancer patients with bone metastasis. *Prostate Cancer Prostatic Dis*. 2011;14:248-252.
5. Huang SP, Bao BY, Wu MT, et al. Impact of prostate-specific antigen (PSA) nadir and time to PSA nadir on disease progression in prostate cancer treated with androgen-deprivation therapy. *Prostate*. 2011;71:1189-1197.
6. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med*. 2004;351:1513-1520.
7. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351:1502-1512.
8. Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol*. 2008;26:242-245.
9. Berthold DR, Pond GR, de Wit R, Eisenberger M, Tannock IF; TAX 327 Investigators. Survival and PSA response of patients in the TAX 327 study who crossed over to receive docetaxel after mitoxantrone or vice versa. *Ann Oncol*. 2008;19:1749-1753.
10. Berthold DR, Pond GR, Roessner M, de Wit R, Eisenberger M, Tannock AI; TAX-327 investigators. Treatment of hormone-refractory prostate cancer with docetaxel or mitoxantrone: relationships between prostate-specific antigen, pain, and quality of life response and survival in the TAX-327 study. *Clin Cancer Res*. 2008;14:2763-2767.
11. Petrylak DP, Ankerst DP, Jiang CS, et al. Evaluation of prostate-specific antigen declines for surrogacy in patients treated on SWOG 99-16. *J Natl Cancer Inst*. 2006;98:516-521.
12. Sonpavde G, Pond GR, Berry WR, et al. The association between radiographic response and overall survival in men with metastatic castration-resistant prostate cancer receiving chemotherapy. *Cancer*. 2011;117:3963-3971.
13. Langsteger W, Balogova S, Huchet V, et al. Fluorocholine (18F) and sodium fluoride (18F) PET/CT in the detection of prostate cancer: prospective comparison of diagnostic performance determined by masked reading. *Q J Nucl Med Mol Imaging*. 2011;55:448-457.
14. de Bono JS, Scher HI, Montgomery RB, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin Cancer Res*. 2008;14:6302-6309. Erratum in: *Clin Cancer Res*. 2009;15:1506.

Discussion: Biomarkers for Treatment of mCRPC

H&O Is there concern that certain surrogate markers may not be appropriate in certain patients, such as the elderly, as these biomarkers might change over time?

Andrew J. Armstrong, MD, ScM Currently, there are no validated surrogate biomarkers that are acceptable for FDA approval of drugs in metastatic prostate cancer; work is ongoing with CTC changes over time, PFS, and the relationship of these biomarkers to OS. Other endpoints such as pain improvements and prevention or delay of fractures (skeletal events) are not really surrogates, as they directly reflect patient benefit, and these factors are really independent of age. There is no known impact of age on the interpretation of these surrogate biomarkers, including PSA declines with chemotherapy, but the relationship of these markers with survival may be impacted by comorbidities, which can lead to reduction in OS that is not captured by a given surrogate. For example, with bevacizumab and docetaxel, improvements in PFS but not survival were noted; this lack of OS benefit could be explained by comorbidities that increased the risk of death from non–prostate cancer-related causes related to the treatment. It is certainly possible that these surrogate markers need to be interpreted in the context of the disease state, mechanism of action of a drug, and the comorbidities of a man with metastatic disease.

H&O What is your experience in recommending immunotherapy to mCRPC patients?

Anna C. Ferrari, MD In my experience, patients are not perturbed by the idea of receiving a vaccine to treat prostate cancer. On the contrary, many patients come to my practice because they like the idea of stimulating their own immune system rather than receiving cytotoxic chemotherapy. Also, I have many years of experience with sipuleucel-T, so I am accustomed to the fact that there will be little or no tumor regression with this treatment. This fact must also be explained to patients, so that they understand that a sizable amount of time will be needed to achieve a benefit.

David I. Quinn, MD Many men facing the decision of initiating immunotherapy are greatly helped by having a partner with whom they can discuss this decision. Often, a man may initially be resistant to a different type of treatment. Thus, a certain education process is necessary, especially because immunotherapy is a unique approach.

H&O What is your experience in trying to assess molecular markers, such as the androgen receptor or the tumor suppressor PTEN, in mCRPC?

David I. Quinn, MD Clearly, certain genetic changes occur early in the disease process. For example, certain splice variants of the androgen receptor may be present in the initial stages of prostate cancer. With current treatment strategies, many patients go several years, even decades, between initial therapy and the development of mCRPC. The question is how representative the primary tissue is of the eventual metastasis, the tumor microenvironment, and CTCs. These questions still need to be explored. Future trials should try to prospectively collect as many specimens as practical in order to answer these questions. Such samples will allow investigators to associate later treatment responses with early molecular changes.

H&O What impact do biomarker studies have on selecting patients to receive immunotherapy?

David I. Quinn, MD Unfortunately, biomarkers for predicting response to immunotherapy have not yet been defined. Exploration of this area is much needed. It is likely that not all mCRPC patients should receive immunotherapy. Alternatively, some patients may benefit from receiving immunotherapy earlier in the disease course. This may be more of a biological question than a biomarker question.

Anna C. Ferrari, MD While predictive biomarkers for immunotherapy have yet to be identified, the clinical prognostic factors that are typically used may provide much information. For example, extensive metastatic disease, poor performance status, or other combinations of factors that would predict a short OS time (<6 months) would suggest that immunotherapy would not have sufficient time to provide a benefit.

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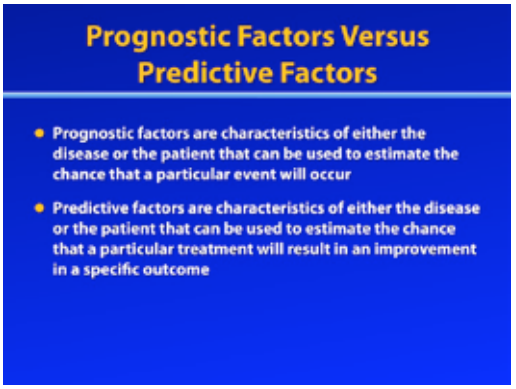

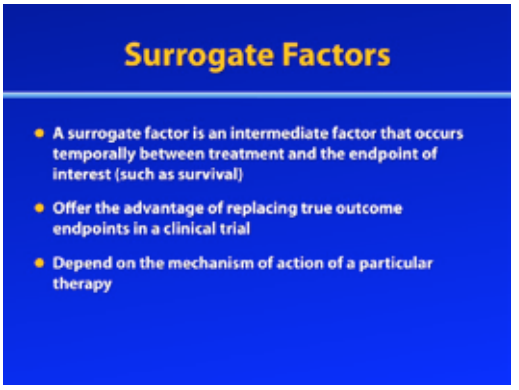

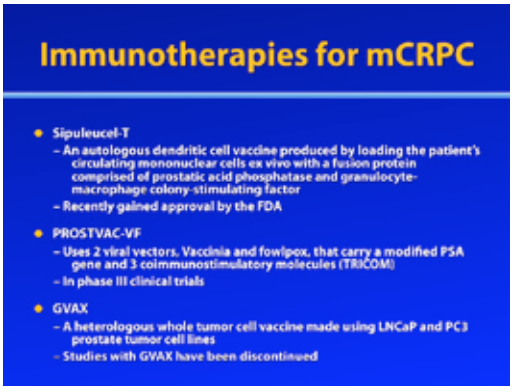

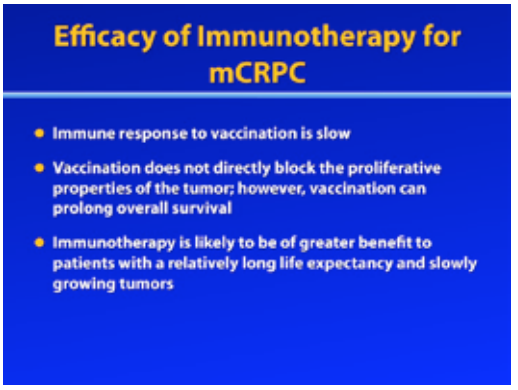

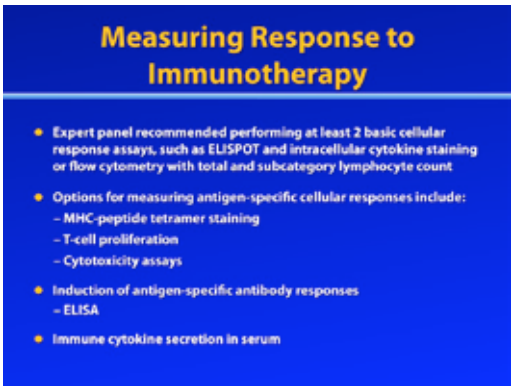

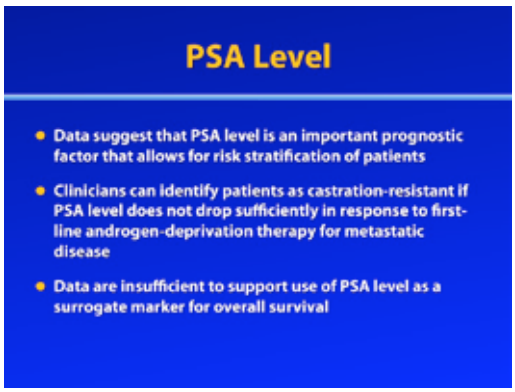

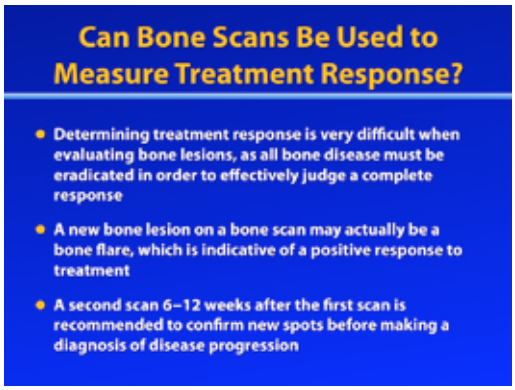

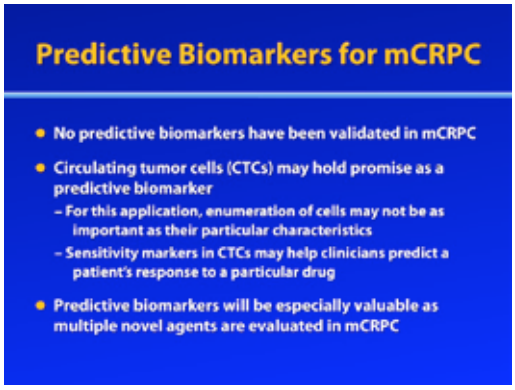

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The Role of Surrogate Markers in the Management of Men With Metastatic Castration-Resistant Prostate Cancer

CME Post-Test: *Circle the correct answer for each question below.*

1. According to retrospective data from the SWOG 99-16 study, which of the following measures of PSA decline following treatment initiation was NOT strongly associated with survival?

   a. 3-month PSA declines of 20–40%
   b. 2-month PSA declines of 30%
   c. PSA velocity at 1 month
   d. PSA velocity at 2 months

2. In a 2007 analysis of the TAX 327 trial, which of the following was associated with the highest degree of surrogacy?

   a. Decline in PSA level of at least 15% within 1 month of initiating treatment
   b. Decline in PSA level of at least 15% within 3 months of initiating treatment
   c. Decline in PSA level of at least 30% within 3 months of initiating treatment
   d. Decline in PSA level of at least 30% within 6 months of initiating treatment

3. Data presented by Scher and colleagues at the 2011 American Society of Clinical Oncology Annual Meeting showed that the number of circulating tumor cells was significantly associated with which endpoint?

   a. Time to progression
   b. Progression-free survival
   c. Stable disease
   d. Overall survival

4. Of patients in the TAX 327 trial who had significant pain at baseline, how many experienced a pain response that was prognostic independent of treatment effect?

   a. 15%
   b. 22%
   c. 29%
   d. 37%

5. Sipuleucel-T gained approval by the US Food and Drug Administration based on which of the following findings?

   a. Significant reduction in tumor size
   b. Significant increase in progression-free survival
   c. Significant increase in overall survival
   d. Significant reduction in pain

6. Which of the following is NOT a factor clinicians need to consider when implementing immunotherapy?

   a. Immunotherapy improves quality of life but not overall survival
   b. Traditional measures of response such as RECIST and bone scans may not be useful with immunotherapy
   c. An effective immune response against a tumor requires time to develop
   d. The proliferative properties of the tumor are not directly blocked by vaccination, so the tumor continues to grow

7. Which of the following endpoints can be used to evaluate treatment response and predict outcomes following immunotherapy?

   a. RECIST
   b. Bone scans
   c. PSA levels
   d. None of the above

8. Which of the following patients have the worst outcomes?

   a. Patients with visceral metastases involving the liver, spleen, or brain
   b. Patients with pulmonary metastases
   c. Patients with only lymph node or bone metastases
   d. Distribution of metastases has no effect on outcomes

9. According to a 2006 study by Hussain and colleagues, what PSA level is a strong predictor of survival among hormone-naïve prostate cancer patients with metastatic disease who initiate androgen-deprivation therapy?

   a. 4 ng/mL or lower after 3 months of therapy
   b. 4 ng/mL or lower after 7 months of therapy
   c. 5 ng/mL or lower after 3 months of therapy
   d. 5 ng/mL or lower after 6 months of therapy

10. According to many new study protocols, what should clinicians do after detecting progression on a bone scan, assuming there are no other indicators of clinical progression?

    a. Have a second radiologist confirm interpretation of the results
    b. Immediately repeat the bone scan to confirm the presence of new lesions
    c. Perform a second scan 6–12 weeks later to confirm the presence of additional new lesions
    d. Progression should never be diagnosed based on bone scans

Project ID: 8568

Evaluation Form: The Role of Surrogate Markers in the Management of Men With Metastatic Castration-Resistant Prostate Cancer

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objectives
After participating in this activity, I am now better able to:

1. Identify possible roles of surrogate markers in determining treatment efficacy in mCRPC	1 2 3 4 5
2. Assess the impact and merit of immune system activation and immunotherapy in mCRPC	1 2 3 4 5
3. Discuss biomarkers and their role in the assessment and treatment of patients with mCRPC	1 2 3 4 5

Based upon your participation in this activity, choose the statement(s) that apply:
❒ I gained new strategies/skills/information that I can apply to my area of practice.
❒ I plan to implement new strategies/skills/information into my practice.
❒ I need more information before I can implement new strategies/skills/information into my practice behavior.
❒ This activity will not change my practice, as my current practice is consistent with the information presented.
❒ This activity will not change my practice, as I do not agree with the information presented.

What strategies/changes do you plan to implement into your practice? _____

_____

How confident are you that you will be able to make this change?
❒ Very confident ❒ Unsure
❒ Somewhat confident ❒ Not very confident

What barriers do you see to making a change in your practice? _____

_____

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

The content presented:

Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
Promoted improvements or quality in healthcare	1 2 3 4 5
Was scientifically rigorous and evidence-based	1 2 3 4 5
Avoided commercial bias or influence	1 2 3 4 5
Provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc)	1 2 3 4 5
My opportunity for learning assessment was appropriate to the activity	1 2 3 4 5

Handout materials were useful: ❒ Yes ❒ No ❒ No handouts for this activity

Would you be willing to participate in a post-activity follow-up survey? ❒ Yes ❒ No

Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

_____

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 8568**. Upon successfully registering/logging in and completing the post-test and evaluation, your certificate will be made available immediately.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Request for Credit (*required fields)

Name* _____ Degree* _____

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For Physicians Only: I certify my actual time spent to complete this educational activity to be:
❒ I participated in the entire activity and claim 1.25 credits.
❒ I participated in only part of the activity and claim _____ credits.