

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Biomarkers in Castration-Resistant Prostate Cancer



Andrew J. Armstrong, MD
Associate Professor of Medicine and Surgery
Duke Cancer Institute
Divisions of Medical Oncology and Urology
Duke University
Durham, North Carolina

H&O Could you please provide a brief overview of biomarkers?

AA A biomarker is an objectively measured and quantifiable biologic characteristic that can indicate a normal biologic process, a pathologic process, or a response to a therapeutic intervention. Broadly speaking, a biomarker can refer to a blood test, a response to a validated questionnaire, an oncogenic mutation, a radiographic measurement, a pain assessment, or a pharmacodynamic measurement.

Biomarkers can be prognostic, predictive, pharmacodynamic/mechanistic, or surrogate in nature, or they can serve multiple roles. In oncology, biomarkers can be useful in providing feedback to inform on patient prognosis, to identify the most suitable therapy for a patient, to determine whether a treatment is hitting the correct molecular target, and to determine whether a treatment is providing clinical benefit. When discussing the utility of a biomarker, it is important to use the correct terminology and to not confuse prognostic with predictive value.

A prognostic biomarker is a natural history biomarker that suggests the likely outcome of a disease independent of treatment. More than 20 validated prognostic biomarkers exist in castration-resistant prostate cancer (CRPC), including prostate-specific antigen level, Gleason score, pattern of spread of disease, circulating tumor cell (CTC) enumeration, lactate dehydrogenase levels, and pain. These do not necessarily tell you how to treat a specific patient, but they can help offer a sense of the prognosis for that patient in terms of expected survival, the timing of onset of symptoms, and the probability of response to a range of therapies. We now use computer algorithms (nomograms)

to examine a range of biomarkers simultaneously to understand in a very complex way the prognosis of patients with metastatic CRPC. Examples of these software programs can be found as online applications, including a predocetaxel and postdocetaxel CRPC nomogram available for iPhone and iPad (<https://itunes.apple.com/us/app/crpc-nomogram-app/id711575978?mt=8&ls=1>) and another recently published postdocetaxel CRPC nomogram that is available through the Duke Cancer Institute website (<https://www.cancer.duke.edu/Nomogram>).

A second category for biomarker use is the predictive biomarker. A predictive biomarker is a disease or host characteristic that estimates the chance of improved outcomes with a particular treatment. In breast cancer, overexpression of the human epidermal growth factor receptor 2 (HER2) oncogene is a recognized predictive biomarker that is adversely prognostic and that also positively predicts benefit with trastuzumab (Herceptin, Genentech) and other HER2-directed therapies. Oncology now has many examples of clinically useful predictive biomarkers, including epidermal growth factor receptor (EGFR) mutations in non-small-cell lung cancer that predict benefit from EGFR inhibitors, *RAS* mutations in colorectal cancer that predict lack of benefit from EGFR monoclonal antibody therapy, and clear-cell histology in renal cell carcinoma that predict benefit from high-dose interleukin-2 immunotherapy.

However, in metastatic CRPC, qualified predictive biomarkers have been largely lacking thus far. All therapies approved by the US Food and Drug Administration (FDA) for use in men with CRPC were developed in unselected populations without biomarker enrichment,

and efforts thus far to identify validated pretreatment characteristics that determine improved outcomes in a biomarker-defined subset of men with any of our approved therapies are not yet available. Given the number of newly approved and expensive systemic therapies (including novel hormonal therapies, chemotherapies, immunotherapies, and bone microenvironment–targeting therapies), predictive biomarkers are clearly needed to help oncologists match specific patients to the right therapy sequence while also minimizing toxicities.

The third category of use is a surrogate biomarker, which estimates the treatment effect as an intermediate endpoint for a gold-standard outcome, such as survival. A uniform surrogate biomarker has not been established in CRPC, but this is an important area of research. Some important biomarkers under study as surrogates include CTC enumeration and radiographic progression-free survival (PFS). However, studies to date have not established this surrogacy across multiple trials. A case that exemplifies the complexity of establishing surrogacy is the improved survival with sipuleucel-T immunotherapy in men with metastatic CRPC, in which PFS was not improved, and the converse scenario of improved PFS with docetaxel plus bevacizumab (Avastin, Genentech) in men with metastatic CRPC, in which PFS was improved but OS was not. Establishing a surrogate is a challenging task that requires positive outcomes in multiple large phase 3 studies. In addition, these surrogates need to be measured and quantified in a reproducible way and have a strong statistical association with such outcomes. Furthermore, the surrogates are likely dependent on the mechanism of action of the drug under study.

The last category of use is a pharmacodynamic biomarker, which is utilized to understand the mechanism of action of a therapy. These are often measured at the tissue level but may be measured in the serum or blood to tell us how drugs are affecting the body, and how the body is affecting the drug.

H&O What components are involved in biomarker validation?

AA Biomarker validation is much like the drug development process. It can be considered in 3 steps prior to large-scale clinical testing: (1) preanalytical assessment of biologic rationale and mechanism, along with specimen selection, handling, processing, and storage parameters; (2) validation of analytical characteristics to meet Clinical Laboratory Improvement Amendments (CLIA) regulatory requirements; establishing interassay and intraassay precision, linearity, analyte recovery, and standardization; and developing a comprehensive quality control program; and (3) postanalytic parameters such as optimal thresh-

olds, optimal patient populations, and test performance in negative and positive control populations.

After assay development and optimization (phase 1), a biomarker can then move to phase 2 testing. Phase 2 testing, which involves a larger number of patients, allows assay variability and optimization to be established and the appropriate settings (prevalence, context of use) to be determined. A successful biomarker that passes these hurdles can then be ascertained retrospectively in clinical trials or it may be prospectively embedded for hypothesis testing research related to prognostic, predictive, pharmacodynamic, or surrogate value. Successful predictive biomarkers could lead to trial designs in which the presence of a biomarker could dictate treatment arms or enrich a patient population for a specific therapy in which patients with a given biomarker clearly have enrichment for benefit and lack of harm from a given therapy. This can lead to the approval of companion diagnostic tests with approved therapies.

Once a biomarker is approved, there is often still much more work to be done in order to figure out exactly which population it should be evaluated in. These are the postapproval phase 4 studies of a biomarker, which determine the best time to order the test, which patient populations are optimal for testing, and the relative cost-effectiveness of different management strategies.

The great news for men with advanced CRPC is that they are living much longer than they did in the past, even without a biomarker-driven paradigm. The median survival for a man with metastatic CRPC prior to chemotherapy is now 3 to 5 years, with many men living longer than that. It takes a very long time to develop drugs and biomarkers in this treatment space, given this long survival duration. An established surrogate biomarker would help identify active drugs without having to wait for nearly half a decade to figure out if the drug works. We now have many active drugs, and it is often very difficult to show a survival benefit because of the number of active therapies that can be used sequentially in these patients.

H&O What is the role of surrogate biomarkers in drug development?

AA For a surrogate to be adequately studied, it has to be part of the drug development process. For example, CTCs have been evaluated in the context of a range of phase 3 studies in order to determine whether the measurement of CTCs (using the FDA-approved CellSearch [Janssen Diagnostics] test) can act as a surrogate test across a range of different drug classes, including hormonal, immunologic, or cytotoxic therapies. Such a result would imply that simply counting the number of CTCs in a single tube of blood provides can provide more information beyond

patient-level prognosis, and could function at a trial level to determine if a drug is effective and can result in long-term improvements in survival. Such data are still under analysis across a range of trials, and while there is no doubt about the prognostic value of CTC enumeration, we do not yet have a universal surrogate for survival in castration-resistant disease that can be used for early drug approval or used in isolation to inform management decisions.

As an example of this, Howard Scher and colleagues recently presented findings during the 2013 European Cancer Congress on the surrogate value of a new biomarker panel. This analysis of the phase 3 COU-AA-301 pivotal trial showed that a biomarker panel of CTC and lactate dehydrogenase measurements taken 12 weeks after starting treatment with either prednisone plus abiraterone acetate (Zytiga, Janssen Biotech) or prednisone alone was able to separate long-term prognosis in men with metastatic CRPC in the postdocetaxel setting, regardless of treatment. Investigators determined that this biomarker panel functioned as a surrogate in this trial, similarly to how we demonstrated that prostate-specific antigen (PSA) declines had some degree of surrogacy after docetaxel therapy. However, further validation studies of this biomarker panel as a surrogate across other settings and in the predocetaxel CRPC space are needed, and it is likely that the thresholds and types of biomarkers included in such a panel may differ in early disease settings.

Surrogates should be measured early in the phase of drug development, and they should be embedded prospectively in phase 3 studies in order to determine whether they will influence the final endpoint and fully capture the effect of an intervention on the efficacy (survival) endpoint.

H&O What is the potential role(s) of predictive biomarkers in CRPC?

AA In castration-resistant disease, there are a number of established key oncogenes that have the potential to be predictive biomarkers.

The first is the androgen receptor itself. It is well known that prostate cancer can synthesize its own androgen and can amplify the receptor, but what may be even more predictive are certain variants of the androgen receptor, where these c-terminal deletion or splice variants have lost the ability to bind to testosterone and to the drugs that block the receptor. Several new agents were developed to more potently block androgen synthesis or inhibit androgen binding to the androgen receptor. Abiraterone acetate and enzalutamide (Xtandi, Astellas Pharma/Medivation) have been shown to improve survival rates of patients with metastatic CRPC in the postdocetaxel setting. It may be that the presence of such androgen receptor variants is

predictive of the lack of benefit with these therapies, and studies are ongoing to assess this.

Other potential genes and pathways in prostate cancer that are commonly activated are the retinoblastoma family of genes, the *RAS* family of genes, and the phosphate and tensin homologue (PTEN)/phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway. Biomarkers of these activated pathways are available and are being assessed prospectively in a range of phase 2 trials of agents that target these key driver genetic lesions in men with CRPC.

Another subtype of CRPC is neuroendocrine prostate cancer (NEPC), also called anaplastic prostate cancer. NEPC represents a small subset of cancers that undergo major genomic changes and are no longer androgen receptor-driven. The increased use of more potent androgen receptor-directed therapy may actually increase the prevalence of NEPC. Many groups are now studying and defining neuroendocrine and other histologically variant prostate cancers, including de novo and transformed NEPC, in which the androgen receptor seems to no longer be operative. Loss of retinoblastoma (Rb), gain of *Aurora A kinase* and *N-myc*, and other genomic lesions are common in NEPC, and trials are ongoing (eg, NCT01799278) to determine the association between these NEPC biomarkers and the benefit to targeted therapies for NEPC. Thus, identifying the biomarkers that may predict for certain targeted therapies will be essential for this disease as well.

H&O What are some promising areas of research?

AA Much of the excitement over the last year has focused on immune checkpoint blockade and immunologic approaches. Sipuleucel-T (Provenge, Dendreon) received approval based on a survival advantage in patients with minimally symptomatic metastatic CRPC. It was the first drug to truly have a label based on symptoms. Radium-223 (Xofigo, Bayer/Algeta) was approved in 2013 with a symptom-based label as well, illustrating that patient-reported symptoms can be used as enrichment biomarkers for identifying subsets of patients most likely to benefit. Further work is needed to objectively measure these symptoms, both for predictive uses and also as a surrogate and approval-based strategy. One example is the pain response trial of cabozantinib (Cometriq, Exelixis), a dual *c-Met*/vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitor in phase 3 testing in men with CRPC.

There are many immunotherapies under development in men with CRPC, including immune checkpoint blockade (ie, CTLA-4 blockade), myeloid suppressor cell inhibitors (the experimental agent tasquinimod), and viral vaccines (ie, Prostavac). A major challenge is identifying predictive and surrogate biomarkers of immunologic

therapies across all disease states. In the future, having adequate readouts for the activated immune system for target expressions will be essential in developing these immune therapies, particularly some of the T-cell therapies that have resulted in dramatic responses in leukemia and that may be applicable in solid tumors.

H&O What are the biggest remaining challenges related to developing biomarkers for CRPC?

AA The biggest remaining challenge is having the investment from industry and granting agencies in the development of predictive and surrogate biomarkers. There is somewhat of a conflict of interest in the development of a drug and a companion diagnostic. When companies develop a drug, they want it to work in the largest population possible, knowing that there are some patients who may not benefit from it. In the development of predictive biomarkers, you are intentionally narrowing the range or the market for a drug to work better in patients who are most likely to benefit. As such, there is an underlying tension between biomarker

development and drug development. Ultimately, however, we are all interested in developing agents that work best in patients who are more likely to benefit and to minimize the cost and harms to patients who are not likely to benefit—I think these aims are intrinsically connected, and that is how they should be viewed.

Suggested Readings

Armstrong AJ, Eisenberger MA, Halabi S, et al. Biomarkers in the management and treatment of men with metastatic castration-resistant prostate cancer. *Eur Urol*. 2012;61(3):549-559.

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