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Biomarkers in the Management and Treatment of Men with Metastatic Castration-Resistant Prostate Cancer

Andrew J. Armstrong[a,*], **Mario A. Eisenberger**[b], **Susan Halabi**[a,c], **Stephane Oudard**[d], **David M. Nanus**[e], **Daniel P. Petrylak**[f], **A. Oliver Sartor**[g], and **Howard I. Scher**[h]

[a]Duke Cancer Institute and the Duke Prostate Center, Duke University, Durham, NC, USA

[b]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA

[c]Department of Biostatistics, Duke University, Durham NC, USA

[d]Georges Pompidou European Hospital, Department of Medical Oncology, Paris and René Descartes University, Paris, France

[e]New York Presbyterian Hospital, Weill Cornell Medical College, New York, NY, USA

[f]Columbia Presbyterian Medical Center, New York, NY, USA

[g]Tulane University School of Medicine, New Orleans, LA, USA

[h]Memorial Sloan Kettering Cancer Center, New York, NY, USA

[*]Corresponding author. DUMC Box 102002, Durham, NC 27710, USA. Tel. +1 919 668 8797; Fax: +1 919 668 7117. andrew.armstrong@duke.edu (A.J. Armstrong).

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Abstract

Context—We have recently witnessed a rapid increase in the number of effective systemic agents for men with metastatic castration-resistant prostate cancer (CRPC), including novel hormonal therapies (abiraterone acetate and MDV3100), immunotherapies (sipu-leucel-T), chemotherapies (cabazitaxel), and bone microenvironment targeting agents (denosumab, radium 223). Given the increasing complexity of treatment decisions for this disease, major research and clinical priorities are (1) finding biomarkers that enable an understanding of the natural history and complex biology of this heterogeneous malignancy, (2) defining predictive biomarkers that identify men most likely to benefit from a given therapy, and (3) identifying biomarkers of early response or progression to optimize outcomes.

Objective—In this review, we discuss existing and potential biomarkers in CRPC and how they may currently inform prognosis, aid in treatment selection (predictive value), and relate to survival outcomes (surrogacy).

Evidence acquisition—PubMed-based literature searches and abstracts through September 2011 provided the basis for this literature review as well as expert opinion.

Evidence synthesis—We address blood and urine-based biomarkers such as prostate-specific antigen, lactate dehydrogenase, total and bone alkaline phosphatase and other bone turnover markers, hemoglobin, and circulating tumor cells in the context of prognosis, prediction, and patient selection for therapy. Given the inherent problems associated with defining progression-free survival in CRPC, the importance of biomarker development and the needed steps are highlighted. We place the discussion of bio-markers within the context of the design/intent of a trial and mechanism of action of a given systemic therapy. We discuss novel biomarker development and the pathway for surrogate or predictive biomarkers to become credentialed as useful tests that inform therapeutic decisions.

Conclusions—A greater understanding of biomarkers in CRPC permits a more personalized approach to care that maximizes benefit and minimizes harm and can inform clinical trials tailored to men most likely to derive benefit.

Keywords

Castration-resistant prostate cancer; Biomarkers; Prognosis; Surrogate; Circulating tumor cells; PSA; Bone turnover markers; Progression-free survival

1. Introduction

In 2010–2011, four systemic therapies demonstrated improved overall survival (OS) in men with metastatic castration-resistant prostate cancer (CRPC) and have become part of the therapeutic arsenal. These include the androgen synthesis inhibitor abiraterone acetate (AA) [1], the immunotherapeutic sipuleucel-T [2], and the taxoid cabazitaxel [3]. In addition, the receptor activator of nuclear factor κ-B ligand (RANKL) inhibitor denosumab demonstrated a delay in the onset of skeletal-related events (SREs) in this setting [4], and the radioisotope radium 223 (^{233}Ra) has demonstrated a survival improvement in men with symptomatic bone metastatic CRPC [5]. Given this rapidly changing landscape [6], the expense of these treatment options, and the number of novel agents in development [7], major priorities for both clinical practice and research include the evaluation of biomarkers able to guide therapeutic decision making. In this review, we provide a framework for understanding and using existing biomarkers in CRPC in clinical practice and discuss methods for evaluating novel biomarkers in research settings to maximize clinical benefit.

A biomarker is defined as a "characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [8]. Thus a biomarker can be a blood test, a response to a validated questionnaire, or radiographic measurements, and it is intended to guide patient management. Biomarkers can be prognostic, predictive, or surrogate in nature, or they can serve multiple roles. A *prognostic biomarker* provides evidence about a patient's eventual outcomes from a disease independent of a given therapy, whereas a *predictive biomarker* estimates the likelihood of response/benefit to a specific therapy in a specific context [9]. In metastatic CRPC, a host of prognostic factors have been reported (Table 1), but qualified predictive biomarkers have not been reported. An example of a predictive biomarker in oncology is overexpression of the *HER2* oncogene in breast cancer, which is adversely prognostic and also predicts benefit with trastuzumab [10]. A *surrogate biomarker* goes further and is able to substitute as an intermediate for a clinically meaningful end point such as OS [11]. To fulfill criteria for surrogacy in oncology, a biomarker must satisfy several key statistical criteria described in detail elsewhere [11–14] and must also be validated across multiple trials of a variety of mechanistically distinct agents [11,12]. However, for a biomarker to become clinically useful, it must also directly inform and/or alter a medical decision and the treatment algorithm based on its result. Although prognostic markers can be helpful, predictive and surrogate biomarkers carry a greater degree of importance given their direct relationship with treatment decision making. In this paper, we review a selection of validated biomarkers in CRPC and discuss their utility in both the clinical and research settings.

2. Evidence acquisition

We conducted a literature search using PubMed and American Society of Clinical Oncology or European Society for Medical Oncology abstracts through September 2011 using the search terms for a given biomarker or therapy and prostate cancer with a focus on castration-resistant metastatic disease. Papers were synthesized by one of the authors (AJA), with input from the other authors as to inclusion or exclusion of relevant publications, and all the authors approved the final manuscript.

3. Evidence synthesis

The following sections focus on the evidence, rationale, advantages, limitations, and recommendations for use and evaluation of blood and urine biomarkers in CRPC rather than the broader landscape of imaging tests and qualitative outcome measures such as pain responses or quality-of-life changes, which are addressed elsewhere [15,16]. Table 1 provides a synthesized list of currently validated prognostic and predictive biomarkers, and Table 2 provides a broad list of potential surrogate biomarkers in CRPC and their advantages/disadvantages for clinical applications.

3.1. Prostate-specific antigen and prostate-specific antigen kinetics

It has long been known that serum prostate-specific antigen (PSA) can reflect the burden of disease in men with CRPC [17]; prognostic models include the level of PSA as an independent risk factor for mortality over time [18–20]. Changes in PSA can reflect a reduction in disease burden and clinical benefit with cytotoxic chemotherapy or hormonal agents known to kill tumor cells, and they can have a practical utility in informing and updating prognostic information for an individual patient over time [21–23]. However, several important caveats must be considered in the interpretation of PSA changes over time with effective systemic therapy, particularly drug mechanism. For example, sipuleucel-T is known to improve survival without having an impact on early PSA levels, whereas docetaxel's improvement in OS correlates for the most part with PSA declines within the

first 3 mo of therapy [2]. PSA values may rise following effective systemic treatment prior to declining. Thus interpreting PSA declines in the context of novel immunologic or cytostatic targeted therapies must be done with caution based on proposed mechanism of action (cytostatic, cytotoxic, hormonal, immunologic, differentiating, etc.) and may also depend on the time of sampling [24].

For cytotoxic therapies such as docetaxel, a >30% PSA decline within 3 mo of treatment initiation were determined to be an optimal threshold for the association with OS in two retrospective analyses of large randomized studies [21,22]. However, this threshold and the conventional ≥50% confirmed PSA decline threshold did not demonstrate consistent surrogacy for survival across these trials and thus is not an approvable regulatory approval end point for systemic therapies in CRPC. These associations require prospective surrogacy evaluation [15,23]. In addition, PSA progression during CRPC therapy was also shown to be prognostic for OS but likewise is not a surrogate for OS [25,26].

Based on these analyses, the updated Prostate Cancer Working Group (PCWG2) guidelines do include PSA changes and progression metrics as reportable outcomes but do not recommend that these changes be used as the sole end point on which to base decisions to change therapy or declare treatment failure/progression, and they recommend reporting of PSA changes descriptively as part of a waterfall plot [15,27]. Given the weak association between early isolated PSA rises and survival, the PCWG2 does not advise stopping therapy for early PSA changes alone [28]. PCWG2 advises reporting outcomes of each disease manifestation such as PSA separately so that the association between the change in each of the manifestations can be studied independently [15]. In this context, baseline and regular (per cycle or monthly) assessment and reporting of PSA levels during therapy and clinical trials of men with metastatic CRPC are recommended.

PSA doubling time (PSA DT) or velocity is also prognostic for OS in CRPC, similar to other earlier disease states of prostate cancer (PCa). In nonmetastatic CRPC, both the PSA DT and the absolute PSA alone can identify men at high risk for early metastatic progression; this risk exists along a continuum, representing both the burden and pace of the underlying tumor [29,30]. In metastatic CRPC, PSA and PSA DT are independently prognostic for OS, and reductions in PSA velocity (half-life dynamics) with docetaxel-based therapies suggest a more favorable prognosis over time [17,18,21,22,31]. In men with asymptomatic metastatic CRPC, rapid PSA kinetics is a poor prognostic finding and may suggest a need for aggressive therapy such as docetaxel to prevent the onset of symptomatic disease [18,20]. However, caution is advised in interpreting PSA DT over time because these changes have not been formally evaluated prospectively for surrogacy for OS in phase 3 trials, and PSA DT may change naturally over time without intervention [21,22,32]. Finally, recent findings suggest a direct effect of docetaxel on androgen receptor (AR) dynamics and therefore likely on PSA production [33]. However, given the benefits of docetaxel chemotherapy in men with CRPC in terms of survival and palliation and in cancers that do not depend on AR signaling, it is likely that this AR effect is not solely responsible for docetaxel efficacy, and other measures of efficacy such as radiographic changes and pain response may better capture this cytotoxic effect.

To complicate matters during clinical care, early rises in PSA are known to occur during systemic chemotherapy administration in 15–20% of men with CRPC; however, these transient changes do not carry an unfavorable prognosis [34,35]. Early PSA rises may reflect a lag in the observation of treatment effect or a transient circulatory release of PSA; most of them occur during the first 3 mo of chemotherapy. Practically, these isolated early PSA changes indicate that stopping a systemic therapy based on PSA alone may be premature and could deprive a man of potentially effective systemic therapy. Providers should discuss

early PSA changes with patients in the context of the mechanism of a given drug, overall clinical picture (pain, radiographic changes), the need for confirmatory PSA evaluations, and the frequent lack of association between patient benefit and early PSA alterations [15].

It should be mentioned that some PCa produces little if any PSA, particularly those with neuroendocrine/small cell histology. In these cases, PSA alterations do not correlate well with clinical benefit, and other biomarkers or measures of response (eg, chromogranin A levels, radiologic, circulating tumor cells [CTCs], symptom relief) should be explored [36,37]. Although chromogranin A levels have been established as independently prognostic in large multivariable models [38], they have not demonstrated predictive value for platinum sensitivity [39], and further studies in the context of other response biomarkers is necessary.

3.2. Circulating tumor cells

The process of hematogenous metastases in PCa likely involves a period of circulatory spread of invasive carcinoma cells followed by establishment of an extravasated colony in the preferred target organ, typically bone in CRPC. The measurement of these rare tumor cells in the circulation of patients with cancer has been studied for >140 yr, but only recently has technology advanced to the point of regulatory approval as a readily available prognostic biomarker [40,41]. The current definition cleared by the US Food and Drug Administration (FDA) of a CTC is a nucleated cell >4 μm in diameter isolated from whole blood using an EpCAM-based ferromagnetic antibody (directed against an epithelial cell surface protein found in many carcinomas), and further defined by lack of the leukocyte marker CD45 and expression of pancytokeratin [40]. CTCs by this definition are not detectable in people without cancer, and the enumeration of CTCs from whole blood has been shown to be prognostic for OS in many tumor types including metastatic CRPC [42]. For example, the finding of five or more CTCs prior to the initiation of cytotoxic chemotherapy is associated with inferior OS similar to that of substantial pain or visceral metastases in CRPC [18,42]. In addition, a drop in CTCs below five has been associated with improvement in OS, similar to the benefit seen with a substantial PSA decline or partial radiographic response [21,22,42,43]. CTC alterations often precede PSA changes, and flares in CTCs have not been reported; thus CTC enumeration and changes over time may be particularly useful when PSA or bone scan changes are difficult to interpret for therapeutic decision making [16]. However, this use has not been prospectively qualified and thus is speculative; the FDA clearance of this test states that it be used as an aid to monitor men with metastatic CRPC in conjunction with other clinical assessments of response/benefit. Finally, recent studies of AA have suggested that changes in CTCs over time may reflect clinical benefit (survival) and serve as a potential surrogate biomarker [44]. A key remaining question is the degree to which CTCs provide a greater degree of association with OS than PSA or radiographic changes over time [21,43]. Whether CTC enumeration as a surrogate can be qualified as a useful biomarker or as part of a biomarker response profile in clinical trials of men with CRPC awaits ongoing prospective phase 3 studies of several novel agents with a wide range of mechanisms (MDV3100 AFFIRM, NCT00974311; TAK-700, NCT01193257; and ipilimumab, NCT01057810) [16].

It is important to recognize there are many potential CTC biomarkers. One caveat with CTC detection using the current CellSearch® epithelial cell–based capture method is the lack of detection in many men (>50%) with CRPC in the predocetaxel setting despite progressive metastatic disease, limiting clinical utility [42,16,45]. This issue becomes critical in the setting of CTC biomarker development. Because CTC visualization may enable a direct measurement of the underlying tumor biology and can be used to assess biomarkers directly in tumor cells, enhanced capture of CTCs may assist in development of predictive biomarkers enabling the personalized tailoring of therapy based on a patient's tumor profile. For example, identification of AR amplification [46,47] or phosphatase and tensin homolog

loss in CTCs [48] suggests that individualized biomarker-driven therapy directly against the AR or PI3 kinase pathway may be possible [48]. Recent findings additionally suggest heterogeneity in the CTC population, leading certain metastatic cells to escape detection mediated through the loss of epithelial markers and the upregulation of mesenchymal and stemness biomarkers [49]. The acquisition of an epithelial-mesenchymal transition or stemness phenotype may explain the relative underdetection of CTCs in many solid tumors, including CRPC [49–51]. Thus improvements in methods for CTC capture through novel CTC chip designs, capture antibodies (mesenchymal antigens, based on prostate-specific membrane antigen), or flow cytometric approaches for improved characterization may enable exploration of CTCs as predictive biomarkers [52–54]. Identification of a greater number or broader phenotypic representation of CTCs should improve target discovery for therapeutic interventions.

3.3. Bone turnover biomarkers

PCa has a well-known propensity for bone metastasis, perhaps mediated through acquisition of osteomimicry properties or adhesion molecules that allow attachment to the bone microenvironment [49,55–58]. As such, agents such as zoledronic acid and denosumab that interfere with this tumor–bone stromal interaction have shown significant delays of important clinical SREs, such as pathologic fracture, radiation/surgery to bone, and spinal cord compression [4,59]. The effects of PCa bone metastases can be indirectly ascertained through a measurement of bone turnover markers, notably the bone type 1 collagen breakdown product N-telopeptide (urine/serum Ntx) and other markers such as tartrate-resistant acid phosphatase 5b, serum type 1 C-telopeptide, osteopontin, and other markers as a measure of osteoclast activation or bone alkaline phosphatase (BAP; a component of total AP) as a measure of osteoblastic activity [60–63]. Although BAP levels have long been known to be prognostic in CRPC, only recently has Ntx emerged as a potential prognostic biomarker in this disease [18,19,60,64]. Persistent activation of Ntx is observed despite zoledronic acid therapy in many men with bone metastatic CRPC, and RANKL antagonism with denosumab has demonstrated reduction in these bone turnover markers, accompanied by superiority in the prevention of SREs when compared with zoledronic acid [4,60].

Effective cytotoxic or radiopharmaceutical therapy can result in a reduction in bone turnover makers by reducing tumor burden; reductions in alkaline phosphatase (AP) with docetaxel, for example, have been shown to be independently prognostic in CRPC, and ^{233}Ra has demonstrated an independent ability to reduce bone AP [39,65,66]. Thus reduction in AP with docetaxel may provide evidence of a survival benefit in the absence of a substantial PSA decline or radiographic response. Several systemic agents are in clinical trials for men with CRPC currently that have a direct impact on this tumor–bone stromal interface, such as the src kinase inhibitor dasatinib [67]. Combination bone-targeted strategies are needed given the modest single-agent and even dual-agent activity seen to date [68]. In conclusion, measurement of baseline and serial levels of AP (total or bone) provides prognostic information across a wide range of systemic therapies. However, whether elevated measures of bone markers predict for the benefit of bone-targeting anticancer agents remains to be demonstrated.

3.4. Lactate dehydrogenase

The metabolic enzyme lactate dehydrogenase (LDH) is part of the normal cellular glycolysis and gluconeogenesis pathway, generating lactate from pyruvate and vice versa depending on cellular energy needs. LDH becomes active in tumor cells through multiple oncogenic mechanisms that foster the Warburg effect, producing lactate through aerobic glycolysis pathways that are favored by cancerous proliferative cells [69]. LDH is an independent prognostic biomarker in many tumor types, including CRPC, and elevations are thought to

be reflective of the underlying tumor burden or an aggressive phenotype [19,64]. LDH can also be increased during oncogenic signaling, hypoxia, or tissue necrosis/injury, and it may reflect a rapidly growing tumor that is outpacing its own drug supply. Its clinical utility as a biomarker of aggressiveness in CRPC lies in this strong prognostic value, reflected in current prognostic models that may help stratify randomization of patients for clinical trials or use prognosis for decision making in the clinic. The composite use of LDH with other biomarkers, such as PSA or CTC enumeration, may also provide evidence for improved risk stratification and prognostication [44]. Finally, although baseline LDH is strongly prognostic in multivariate models in CRPC, increases in LDH following therapy carry an unfavorable prognosis and may be useful in interpreting treatment response [70]. Thus, given the strong independent prognostic association of LDH with OS in CRPC over time, we recommend serial measurement and reporting of this factor during treatment and in the context of clinical trials.

3.5. Hemoglobin

The clinical consequences of PCa bone and bone marrow metastases are often brought to clinical attention through the development of bone marrow suppression, including anemia. Anemia may be a consequence of long-term androgen-deprivation therapy, renal disease, chemotherapy toxicity, anemia of chronic disease, iron deficiency from blood loss (ie, hematuria), bone marrow infiltration, or other coexisting illnesses in men with CRPC. The degree of anemia was found to correlate with prognosis >40 yr ago and has been included in nearly every prognostic model in CRPC to date, including modern nomograms in the docetaxel era and following docetaxel therapy [18,19,64,70–72]. In multivariable analysis, anemia was found to be among the strongest prognostic factors both for docetaxel-related PSA declines, tumor response rates, and overall survival in CRPC. This prognostic variable is included in a CRPC risk-based classification score (anemia, progression by bone scan, visceral metastases, and significant pain) [73]. Thus anemia reflects both the burden of PCa as well as host response, and development of anemia remains a clinically relevant prognostic factor in men with CRPC.

3.6. Can biomarkers improve on the problem of defining progression-free survival in castrate-resistant prostate cancer?

A major clinical and research dilemma in CRPC has been to define and standardize progression as an objective end point and therefore optimize duration of therapy of a given systemic agent. Given the difficulties in interpreting biomarkers and radiographic changes as true measures of PCa progression, rigorous collection and evaluation of these biomarkers as they relate to progression-free survival (PFS) and OS is critical. Given the imperfect relationship of PSA and other biomarkers to measures of progression and survival, technetium Tc 99m radionucleotide bone scans are commonly used to interpret progression/response during systemic therapy for men with metastatic CRPC. However, bone scans typically image osteoblastic activity in bone at a given point in time, and thus they may image both pathologic bone formation and bone healing (ie, fracture) or inflammatory arthritis and can be relatively nonspecific. Bone scan flares are reported to occur commonly with active hormonal agents such as AA and may commonly occur with other systemic agents [74]. These flares are commonly misinterpreted on clinical radiologic reports of bone scans as progression, and discordance between clinical reports and patient benefit was reported in up to 50% of men treated with AA [74]. Early bone scan changes (loss of signal/detection of metastasis) may be quite dramatic with other classes of agents (such as XL184, a c-met/vascular endothelial growth factor receptor 2 tyrosine kinase inhibitor) [75]. However, correlation of bone scan changes with survival has been relatively weak in the published literature in CRPC [25,28,75–77]. This correlation can be depicted through a plot of the hazard ratios for OS against PFS using older definitions of PFS in published phase 3

trials of men with CRPC that typically did not account for transient worsening of either PSA or bone scan findings (Fig. 1). These PFS definitions were often composite and included the earliest of PSA, radiographic, or pain/clinical progression or death, and they did not conform to PCWG2 criteria for determining PFS [15]. As depicted in Figure 1, a strong relationship (linear) between PFS and OS only exists for hormonal therapies (ie, AA) or taxane-based cytotoxic chemotherapy. However, for immunologic or antiangiogenic therapies, there is a striking and opposite correlation between PFS and OS. Sipuleucel-T and Prostvac improved OS without a noticeable change in PFS (using older criteria), whereas bevacizumab and sunitinib improved PFS without an improvement in OS [2,76–78]. Thus mechanism of action must be strongly considered in interpreting surrogacy end points, including PFS and biomarker changes over time. For a biomarker to become a broad surrogate clinical end point, it must be prospectively evaluated in the context of clinical trials that specifically address the biomarker question in this context and across a range of systemic therapies found to have a strong correlation with OS.

3.7. Novel biomarkers: how to qualify a biomarker for regulatory approval

Although a host of prognostic biomarkers are known in CRPC, only a small number are being considered for predictive use, and only CTCs are under formal surrogacy evaluation in clinical trials (Table 3). Predictive biomarkers have the potential to select or enrich for groups of men with CRPC most likely to benefit from a given systemic agent, whereas surrogate biomarkers have the promise of accelerating drug development through early identification of active systemic agents (ie, CTC or PSA declines). A number of clinical trial designs are available that permit for the assessment of treatment effect in enriched populations based on predictive biomarkers [79]. All biomarkers, but particularly predictive and surrogate biomarkers, must be evaluated in a series of well-defined clinical trials to generate qualifying evidence for a specific context of use before incorporation into the approval process for drug development [12]. This pathway depends on the context of use of a given biomarker, encompassing screening/diagnosis, prognosis, prediction of benefit of a specific therapy, pharmacodynamic (mechanistic) measures of treatment response or resistance, and surrogacy. Steps for biomarker validation and qualification involve steps akin to the development of a drug in oncology and include initial stages of development prior to final large-scale pivotal trials [54].

The initial step of oncology biomarker development is ideally based on tumor or host biology and grounded in preclinical models of cancer and/or observational/epidemiologic evidence. Biomarkers must be analytically validated through measures of repeatability, robustness, and accuracy (sensitivity, specificity), and characteristics are dictated by performance characteristics of the test itself, storage conditions, stability, inter- and intrapatient variability (signal to noise), and internal and external validity in a variety of data sets and clinical scenarios. Performance characteristics are well established through Clinical Laboratory Improvement Amendments in the United States and outlined in the National Cancer Institute, FDA, and Centers for Medicare and Medicaid Services' Oncology Biomarker Qualification Initiative, part of the overall FDA Critical Path Initiative [80,81]. A full discussion of these steps is beyond the scope of the current review; however, some key points are discussed, and interested readers are referred to additional sources [54,80,81].

For an analytically validated biomarker to inform clinical practice, it must pass through clinical qualification for context of use [81]. Qualification as a surrogate biomarker, for example, must be conducted prospectively as part of several phase 3 clinical trials that each demonstrate an improvement in the desired clinical outcome (ie, OS). Ideally, agents evaluated in these trials would come from a wide range of mechanisms for a surrogate biomarker to be broadly applicable. However, a surrogate biomarker could still be useful in a particular class of drugs, such as hormonal therapies. If established, a surrogate biomarker

can be clinically useful by informing clinical practice and in research studies in several ways. For example, informing early treatment failure should ideally be linked to a change in therapy with resultant improved clinical outcomes, which would not have otherwise been possible with existing tests (such as PSA or radiologic changes). Biomarker-driven management may lead to a reduction in toxicity due to unnecessary/futile therapy and optimize therapy for men most likely to benefit. Finally, surrogate biomarkers must also satisfy other metrics (ease of use and interpretation, availability, and cost effectiveness) before qualification and widespread use. For example, the CTC test (CellSearch) is currently undergoing qualification as part of several clinical trials in CRPC discussed previously [54]. Early results suggest that favorable CTC changes provide strong prognostic information and satisfy several surrogacy criteria in the phase 3 postdocetaxel AA clinical trial. However, the degree of surrogacy of CTC changes, the added improvements in surrogacy over existing measures, and the reproducibility of these findings in other contexts is needed [44]. Although challenging and slow in pace, this line of biomarker research is critical to optimizing the care and delivery of effective therapies into the clinic and therefore must be prioritized.

4. Conclusions

The clinical utility of biomarkers in men with CRPC is context dependent, meaning that usefulness depends on the clinical/translational question (prognosis, prediction, surrogacy, treatment resistance, pharmacodynamic) and how a biomarker will have an impact on clinical decision making for a given systemic therapy. Currently all biomarkers in clinical use have prognostic implications when measured prior to starting therapy, but they have not yet been credentialed as predictive or surrogate markers in the post-treatment setting. Post-treatment PSA and CTC declines and improvements in bone markers also inform prognosis and may be useful in evaluating therapeutic benefit over time as part of a composite clinical assessment. Ongoing randomized studies of active systemic agents with prospectively embedded biomarker-based validation studies are needed to identify the surrogate value of these biomarkers for OS before these can be used for registrational/regulatory purposes or definitive clinical decision making.

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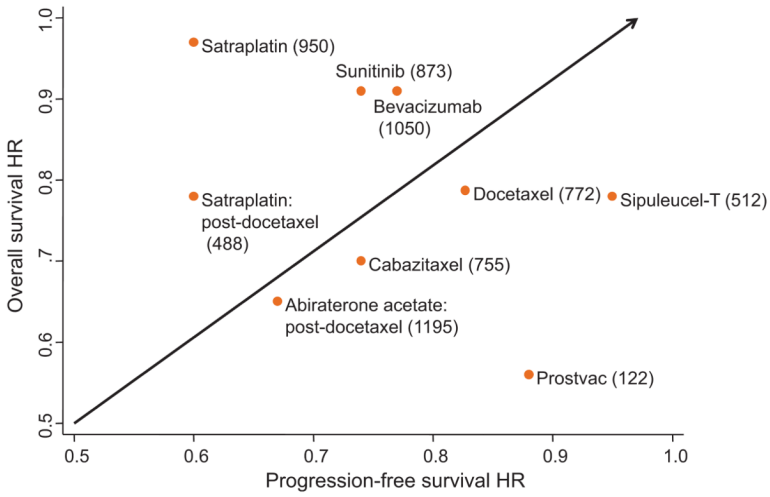

Fig. 1.

The problem of defining progression-free survival (PFS) in castration-resistant prostate cancer (CRPC): the relationship with overall survival (OS) is nonlinear. Plot of the hazard ratios (HRs) for PFS on the x-axis versus OS on the y-axis in large reported phase 3 trials of men with metastatic CRPC that included information on both OS and PFS (typically prostate-specific antigen [PSA] PFS for the majority except Cougar 302, which reported radiographic PFS HR). Note that although differences in PFS definitions existed in these trials, these largely used older definitions did not account for bone scan or PSA flare and often included PSA as part of the progression criteria. The exception to this was the Cougar 301 trial that used the updated Prostate Cancer Working Group PFS criteria. A 1:1 relationship between PFS and OS would fall along the line drawn, which is seen for abiraterone, docetaxel, and cabazitaxel (note this is not a regression line). Immunotherapies (Prostvac, sipuleucel-T) fall below the line, whereas antiangiogenic therapies and satraplatin produced results above the line, indicating discordances between PFS and OS.

Table 1

Prognostic and predictive biomarkers in castration-resistant prostate cancer

Baseline prognostic factors	Prognostic factors post-treatment	Predictive factors
Performance status	PSA declines	None validated
Visceral metastatic disease	Pain improvements	
Anemia	Quality-of-life improvements	
Alkaline phosphatase (bone)	Change in CTC count (≥5 to <5)	
Pain	PSA PFS	
PSA and PSA by RT-PCR	Radiographic PFS	
PSA kinetics	Induction of immunity to tumor antigens (sipuleucel-T)	
Circulating tumor cell count		
Lactate dehydrogenase		
Albumin		
Type of progression (bone, measurable disease, PSA only)		
No. of sites of disease		
Age		
VEGF levels		
Interleukin-6 levels		
Chromogranin-A		
C-reactive protein		
Serum TRAP-5b and other bone turnover markers (sCTX, P1NP, others)		
Gleason sum in primary		
Urine N-telopeptide		

PSA = prostate-specific antigen; CTC = circulating tumor cell; RT-PCR = reverse transcriptase polymerase chain reaction; PFS = progression-free survival; VEGF = vascular endothelial growth factor; TRAP = tartrate-resistant acid phosphatase; sCTX = serum type 1 C-telopeptide; P1NP = procollagen-1 N-terminal telopeptide.

Table 2

Summary of current data supporting changes in biomarkers as potential surrogates for clinical benefit in men with castration-resistant prostate cancer

Biomarker/outcome parameter	Evidence reference	Pros	Cons
PSA declines	Armstrong et al. [21]; Petrylak et al. [22]	Easily measurable Widely available Time <3 mo Evidence to support use with cytotoxic therapy	Not validated with novel agents (ie, PSA-independent benefits) PSA can rise after start therapy in minority Threshold of response unclear Does not allow for unique mechanism of novel agents (immunologic, differentiating, cytostatic) Subgroups of prostate cancer do not produce PSA
Progression-free survival	Halabi et al. [25]; Hussain et al. [26]; Scher et al. [28]	May capture clinical benefit as a delay in pain/tumor growth Improved measure of effect of cytostatic or antiangiogenic agents Flexible definitions	Exact definition is critical Composites likely necessary Lack of validation as surrogate for OS Censorship prevents current surrogate analyses
Pain improvements	Armstrong et al. [21]; Halabi et al. [82]	Direct patient measure	Qualitative thus requires validated scales Many men with CRPC are pain free Subjective, variable, and subject to change with narcotic analgesia alone Not validated Difficult to use as a marker by itself; many causes of pain independent of tumor progression
Bone turnover markers (urine N-telopeptide, bone alkaline phosphatase)	Coleman et al. [60]; Sonpavde et al. [66]	Reflects tumor-stromal interaction and prostate cancer microenvironment Linked to survival in multiple data sets	Normal in patients with visceral-only or node-only disease May be normal even in the face of bone metastases Unclear clinical implications if incompletely suppressed
Quality of life	Berthold et al. [34]	Direct patient measure	Qualitative; thus requires validated scales/measure Defining clinically significant changes Bias is inherent in non–placebo-controlled trials
Radiographic responses (including bone scan changes)	Scher et al. [15]; Sonpavde et al. [43]; Ryan et al. [74]; Scher et al. [83]	Well-defined criteria if measurable disease	No target lesions in patients with increasing PSA and localized disease or bone-only disease Not always measurable soft tissue disease in prostate cancer Modest correlation with overall survival Important treatment effects are missed Bone scan flare can be common, requiring confirmation scans
CTCs	de Bono et al. [42]; Scher et al. [44]	Early detection before PSA rise Allows tumor-specific biomarker assessment within CTCs Strongly prognostic and early signs of validity as surrogate	Only approximately 50% have detectable levels even with widespread metastases using FDA-approved CellSearch platform Not validated as surrogate yet Expensive; performed in specialized labs only; unable to bank/store Quick turnaround necessary due to expiration within 72 h

PSA = prostate-specific antigen; OS = overall survival; CRPC = castration-resistant prostate cancer; CTC = circulating tumor cells; FDA = US Food and Drug Administration.

Table 3

Novel biomarkers with potential clinical utility in development in castration-resistant prostate cancer

Novel biomarker	Potential application in CRPC
Ras/raf mutations	Potential benefit with ras pathway inhibitors (ie, sorafenib, vemurafenib)
Tubulin mutations	Selection of microtubule-based therapies (docetaxel, cabazitaxel)
Absence of significant pain	Selection for sipuleucel-T therapy on label
Androgen receptor splice variants	Predict sensitivity to novel antiandrogens
CTCs	Potential surrogate for overall survival (context dependent)
Cardiac comorbidity	Predict for risk/toxicity with antiangiogenic agents
c-met/HGF activity	Enrich for benefit with c-met inhibitors
Androgen synthesis precursor levels	Predict for benefit from androgen synthesis inhibitors (abiraterone acetate)
PTEN loss in CTCs or metastases	Enrich for benefit with PI3 kinase pathway inhibitors
DNA repair defects (ie, BRCA2 mutations, PTEN loss)	Enrich for benefit with poly-ADP ribose polymerase (PARP) inhibitors
Myc amplification	Cell-cycle inhibitors (antiproliferation agents)
High urine N-telopeptide, TRAP-5b, or other bone turnover markers	Benefit with denosumab or zoledronic acid

CRPC = castration-resistant prostate cancer; CTC = circulating tumor cells; HGF = hepatocyte growth factor; PTEN = phosphatase and tensin homologue; ADP = adenosine diphosphate; TRAP = tartrate-resistant acid phosphatase.