Using Surrogate Biomarkers to Predict Clinical Benefit in Men with Castration-Resistant Prostate Cancer: An Update and Review of the Literature

Andrew J. Armstrong, a Phillip G. Febbo b

a Departments of Medicine and Surgery, Divisions of Medical Oncology and Urology, Duke Comprehensive Cancer Center and the Duke Prostate Center, Durham, North Carolina, USA; b Departments of Medicine and Molecular Genetics and Microbiology, Duke Comprehensive Cancer Center and the Duke Prostate Center, Duke Institute for Genome Science and Policy, Durham, North Carolina, USA

Key Words. Prostate cancer • Surrogate markers • Prostate-specific antigen • src family kinases

Disclosures: Andrew J. Armstrong: Research funding/contracted research: Bristol-Myers Squibb; Phillip G. Febbo: Research funding/contracted research: Bristol-Myers Squibb.

This article discusses the unlabeled, investigational, or alternative use of dasatinib (Bristol-Myers Squibb) and AZD0530 (AstraZeneca) for prostate cancer.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers.

ABSTRACT

Recurrent prostate cancer has a complex molecular etiology and a prolonged disease course. Although initially responsive to androgen ablation, many men eventually become castration resistant, develop skeletal metastases, and are palliatively treated with docetaxel-based chemotherapy, radiation therapy, bisphosphonates, and best supportive care. Given the modest success rates of the current standard of care, clinical trial enrollment is encouraged. Castration-resistant prostate cancer (CRPC) is a heterogeneous disease, both in clinical manifestations and outcomes, requiring an individualized approach to both patient care and trial design. Herein, we review surrogate markers of disease progression and treatment efficacy in advanced prostate cancer in light of recently published guidelines that have redefined eligibility, response criteria, and suitable endpoints in prostate cancer drug development. The guidelines have refined outcome measures to potentially better capture clinical benefit and the ability of novel targeted molecular and biologic agents to impact favorably on this disease. We consider prostate-specific antigen changes, circulating tumor cells, bone scan alterations, markers of bone metabolism (urinary N-telopeptide and bone-specific alkaline phosphatase), pain improvements, and progression-free survival. To illustrate the role and challenges of these potential biomarkers and endpoints in drug development, we discuss a class of novel molecularly targeted agents, the src kinase inhibitors. Given that there are currently no validated surrogate markers of overall survival for assessing early clinical benefit from systemic therapy in metastatic CRPC, incorporation of relevant biomarkers into all phases of clinical development is essential to accelerate drug development in this field. The Oncologist 2009;14:000–000

The Oncologist 2009;14:000–000 www.TheOncologist.com
INTRODUCTION
The identification of active novel agents and docetaxel-based combinations for men with castration-resistant prostate cancer (CRPC) remains one of the major challenges in prostate cancer drug development. Understanding the underlying biology of castration-resistant growth and metastatic progression will undoubtedly deliver agents with a higher probability of success and clinical benefit.

Evolution to a castration-resistant metastatic state involves a complex network of signaling pathways (Fig. 1). The androgen receptor (AR) regulates transcription of a diverse range of genes involved in cell proliferation, differentiation, and apoptosis. AR activation occurs in many cases of CRPC and may result from AR gene amplification, AR mutations, de novo synthesis of androgens, and activation of signaling pathways enhancing AR transcriptional activity, for example, HER2, the epidermal growth factor (EGF) family, members of the phosphatidylinositol-3-kinase pathway, and src family kinases (SFKs) [3, 4]. Therapies capable of inhibiting AR activity by targeting one or more of these processes are likely to provide significant clinical benefits.

Successful novel or combination therapies must demonstrate clinical benefits in phase II trials, and improved survival or a significant impact on an intermediate clinical endpoint in phase III trials. Because of short trial duration and small patient populations, phase II overall survival data are typically not available or sufficiently robust. Interpretation of trial results is often based on comparisons with historical controls using surrogate response-based endpoints for survival. Progression-free survival (PFS), prostate-specific antigen (PSA) declines, and radiologic and pain responses are widely used to estimate clinical benefit for men with CRPC, although additional assessments are increasingly incorporated into trial designs to determine if an agent has a positive impact on underlying disease biology. For example, biomarkers are increasingly being investigated as measures of activity against the tumor or bone-tumor microenvironment. When phase II studies are completed, decisions to move forward with phase III trials are based on aggregate results. Because overall survival is the key endpoint for phase III trials, decisions to move forward with clinical development are often based on suboptimal data and uncertainty.

Recent phase III trials have highlighted this disconnect between phase II and phase III endpoints and the impact on clinical development in CRPC. Ideally, phase II trials should identify inactive compounds prior to initiating larger, more expensive phase III trials. However, atrasentan achieved positive phase II data in men with metastatic prostate cancer (biologic effects on PSA and bone turnover markers), but phase III evaluation was halted early because of failure to delay disease progression [5, 6]. For atrasentan, the use of PSA as a predictive marker proved to be fallible and, at least partly, led to the introduction of new guidelines (see below). Other recent phase III trial failures in CRPC.

Figure 1. The concept of progression in prostate cancer [1, 2]. Abbreviations: AR, androgen receptor; CRPC, castration-resistant prostate cancer; ETS, E26 transformation-specific; GSTP1, glutathione S-transferase pi1.
include GVAX prostate cancer vaccine (stopped because a futility analysis indicated that the trial had a low probability of meeting the primary survival endpoint) and the vitamin D supra-agonist DN101 in the ASCENT 2 trial (stopped because of excessive toxicity) [7–9]. In addition, the platinum compound satraplatin did not meet its overall survival endpoint in phase III despite marginal improvement in a composite PFS endpoint, emphasizing the need for validated trial endpoints, more accurate methods for assessing patient benefit, and agents with more substantial antitumor activity [10].

In this review, we will illustrate the challenges and potential of incorporating surrogate markers into drug development using the development of SFK inhibitors in CRPC. Inhibition of the src signaling pathway has been investigated in several oncology settings. The SFKs are ubiquitous signal transduction and regulation molecules, involved in multiple pathways in prostate cancer, and implicated in tumor cell proliferation, survival, migration, and transition to androgen-independent growth [11, 12]. Src also controls normal and abnormal bone physiology, and has been implicated in development and progression of bone metastases (Fig. 2). The multiple roles of src kinases in normal and pathologic disease processes raise important questions on which criteria should be used to evaluate these and other agents to improve success rates for phase III trials.

**CAN WE APPLY CURRENT GUIDELINES TO ALL CLINICAL TRIALS?**

Systems for appraising responses in prostate cancer trials have been developed and recently updated. The first system was based principally on circulating PSA levels, proposed as a surrogate marker of efficacy/response by the National Cancer Institute first PSA Working Group [14]. The second system was based on responses across all types of solid tumor according to Response Evaluation Criteria in Solid Tumors (RECIST) [15]. Neither system has proved to be a uniformly accurate predictor of efficacy in prostate cancer.

New guidelines have been published recently by the second Prostate Cancer Clinical Trial Working Group (PCWG2) [16]. These guidelines, encompassing revised elements from both the first Working Group (PCWG1) and RECIST, aim to maximize the ability of phase II studies to select promising therapies and inform phase III trial design. Importantly, concepts of hormone insensitivity or refractoriness were replaced by the term “castration resistant,” reflecting that intact AR signaling often occurs even in the later stages of disease progression [16–18]. Dual therapeutic objectives were defined, comprising (a) those based on controlling, relieving, or eliminating existing disease; and (b) those based on preventing or delaying disease development. PCWG2 guidelines suggest that trial eligibility should be defined using standardized assessments to authenticate progressive disease (including PSA “mapping” and confirmation of bone lesions seen on nuclear scanning), taking account of prior treatment history, defining distinct clinical subtypes (based on pattern of disease spread and prior treatment history), and highlighting the importance of predictive/prognostic models, including the future use of surrogate markers once validated [16].

Importantly, PCWG2 guidelines counsel against early reliance on classic response indicators, such as serum PSA decline or bone scan changes, particularly for noncytotoxic biologic agents. Even with cytotoxic agents, because PSA declines are only modest surrogates for the overall survival benefit conferred by docetaxel, PSA measures should be viewed with caution [19]. Compared with conventional chemotherapies, antiangiogenic, cytostatic, or immunomodulatory therapies may work independently of response indicators, or have a delayed onset of action. Therapies that increase differentiation (and slow progression) of prostate cancer may increase PSA levels while reducing tumor volume. With this in mind, the guidelines highlight the importance of avoiding sole reliance on PSA changes during evaluation and allowing a sufficient window of drug exposure, enabling treatment until there is clear clinical or radiologic progression. This provides a greater exposure to potentially active agents and less opportunity to prematurely abandon agents based on potentially spurious biomarker changes. Furthermore, the guidelines advocate a shift from definitive responses at a predetermined time to time-to-event measures [16].

We are currently in a transition period: Phase II trials based on prior guidelines are ongoing, so how should we...
interpret these data? Clearly, caution is needed. Trial endpoints should be aligned to reflect therapeutic objectives, disease subtypes, and type of agent (e.g., conventional cytotoxic or targeted biologic). Endpoint data should be reviewed according to updated guidelines. Although overall survival remains the Food and Drug Administration (FDA) standard for drug approval in CRPC, other measures of patient benefit (pain response, prevention of skeletal related events) are clearly relevant measures that can lead to approvals in this disease (Table 1).

**Which Surrogate Markers Are Currently Used as Study Endpoints?**

**PSA**

Although several prostate cancer-associated antigens have been identified [20], PSA is most commonly used. PSA can be measured routinely throughout clinical testing and responses can be evaluated within months of starting or changing therapy. Initial studies found that a confirmed PSA decline of ≥50% following chemotherapy was highly prognostic and was adapted as an early marker of drug activity in phase II studies [14]. In 2006, a retrospective analysis of the Southwest Oncology Group (SWOG) phase III study identified PSA decline as a potential surrogate marker for overall survival [21]. This was supported by subsequent data from the TAX327 study demonstrating that a PSA decline of ≥30% within 3 months provided the greatest degree of surrogacy for overall survival benefit [22]. However, the degree of surrogacy differed between trials (67% in TAX327 vs 100% in SWOG 9916), possibly relating to estramustine use in the SWOG study, which may increase the correlation between PSA change and survival. Because estramustine is now rarely used in first-line treatment, PSA remains a modest surrogate for survival. Because of the direct relationship between AR activity and PSA production, PSA decline may be a better surrogate for hormonal therapies than for cytotoxic therapies. Given the molecular heterogeneity of prostate cancer in terms of activation of the AR gene expression program, it will be important to evaluate PSA changes in the context of the underlying biology of CRPC. For example, PSA decline may be an excellent surrogate for survival in AR-driven tumors treated with novel hormonal therapies, but not for tumors that are AR-independent [23]. For non--AR-driven tumors, other measures, such as circulating tumor cell (CTC) counts, may be more reflective of patient benefit.

Overall PSA declines are predictive for tumor effects. However, up to 20% of men experience an initial serum PSA increase (PSA flare) before a subsequent decline in responding men [24]. This suggests that early PSA increases within the first 12 weeks of treatment should be ignored in the absence of other signs of clinical progression when determining response or progression [24], although a specific timescale for accurately predicting clinical benefit has not been established. Furthermore, PSA production may not be uniform, particularly in patients with advanced metastatic CRPC, and this is problematic for assessing agents with a novel mode of action targeting a particular phenotype of primary tumor. For example, differentiating agents may cause a rise in PSA with a concomitant reduction in tumor volume, whereas immunomodulatory agents may have a delayed action to stabilize, rather than directly reduce, PSA production and tumor growth [14]. Under these circumstances PSA levels should be measured, but should not be imbued with the same predictive ability attributed to cytotoxic agents such as docetaxel.

**Progression-Free Survival**

Recent retrospective studies have explored the association between PFS, defined on the basis of changes in PSA, pain, or radiographic progression in bone and/or soft tissue, and overall survival [25, 26]. The measures of progression were highly predictive of survival; however, a relatively low association was found between the two variables, suggesting that other physiologic processes involving pathways not measured by changes in bone scans or PSA are involved [27], or that the current definitions used to define progression do not adequately capture patient benefit and survival outcomes. The advantages and disadvantages of PFS as a surrogate of survival in determining novel agent activity have recently been reviewed [28]. An agent, for example, that lengthens PFS but shortens postprogression survival, without altering overall survival, may be much less desirable than an agent that favorably prolongs each endpoint. In addition, composite definitions of progression (i.e., pain and PSA progression) may more clearly reflect the underlying biology of the tumor. Despite this, recent studies in CRPC have been unable to demonstrate a clear relationship between PFS and overall survival [29, 30].

The PCWG2 criteria distinguish two types of objectives for phase II clinical trials. The first is based on controlling, relieving, or eliminating disease manifestations that are present when treatment is initiated and the second, on preventing or delaying future disease manifestations [16]. Because of uncertainties with assessing response in bone and the controversy surrounding the clinical significance of post-therapy changes in PSA, the PCWG2 suggests expanding the focus of phase II trials from measures of response to measures of progression/delay [16]. One caveat to this is that we are equally if not more uncertain as to how

**Published Ahead of Print on August 14, 2009 as 10.1634/theoncologist.2009-0043.**
### Table 1. Outcome measures used in prostate cancer clinical trials

<table>
<thead>
<tr>
<th>Variable</th>
<th>Suggested outcome measure (PCWG1)</th>
<th>Suggested outcome measure (PCWG2)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| PSA          | Partial response as a confirmed >50% decline from baseline                                       | For agents expected to control, relieve, or eliminate tumor cells: percentage change at 12 weeks recorded in a waterfall plot | ● Easily measured  
   ● Availability  
   ● Prognostic for cytotoxic therapy                                                                                     | ● Potential initial rises in PSA after onset of therapy  
   ● Validation is required  
   ● Correlation with noncytotoxic therapies not defined  
   ● Differentiation effects may lead to PSA rises                                                                             |
| Progression  | After an initial decline = 50% increase from nadir and an increase of at least 5 ng/ml          | First increase of 25% and 2 ng/ml above nadir (confirmed by second read)                        |                                                                                                                     |                                                                                                                         |
|              |                                                                                                 | PSA progression defined as >25% and 2 ng/ml after 12 weeks                                      |                                                                                                                     |                                                                                                                         |
| Duration of decline | Measured                                                                                      | Not required                                                                                   |                                                                                                                     |                                                                                                                         |
| Lesions      | Change in lymph nodes or parenchymal mass (physical or x-ray examination)                       | For agents expected to control, relieve, or eliminate tumor cells: RECIST criteria with caveats:  
   ● Lymph nodes ≥2 cm only  
   ● Nodal and visceral sites reported separately  
   ● Record elimination and confirmed favorable changes  
   ● Present data as a waterfall plot                                                                                     | RECIST 1.1 criteria are well defined for measurable disease and more validated                                       | ● Not always applicable to prostate cancer (localized disease, bone-only lesions)  
   ● No correlation with PSA or clinical progression  
   ● Key treatment effects may be missed  
   ● Bone scan flare remarks poorly defined  
   ● Not proven surrogate yet                                                                                               |
| Bone         | No overall definition provided                                                                 | Definition included                                                                              |                                                                                                                     |                                                                                                                         |
| Progression  | >1 new lesion; worsening scan regardless of PSA status                                           | For agents expected to control, relieve, or eliminate tumor cells:  
   ● No new lesions, therapy should continue  
   ● New lesions (confirmed on scan ≥6 weeks later) = progression                                                                 |                                                                                                                     |                                                                                                                         |
|              |                                                                                                 |                                                                                                   |                                                                                                                     |                                                                                                                         |

(continued)
to define progression in prostate cancer as we are in defining response. Despite this, endpoints should reflect the mechanism of action of the agent being studied and should more directly capture patient benefit over time. These changes in definitions of progression will need to be independently validated against overall survival prior to their incorporation as primary endpoints for phase III studies.

**Computed Tomography and Magnetic Resonance Imaging (RECIST)**

In clinical studies, radiologic methods are often used to evaluate objective responses in target lesions in lymph nodes or visceral tissue based on RECIST criteria. However, data are lacking to indicate that RECIST criteria are predictive for survival, possibly reflecting the lower clinical relevance of soft-tissue metastases and bone tropism in prostate cancer compared with other solid tumors [31]. Because early changes in metastatic lesions may not reflect disease status during treatment with noncytotoxic agents, PCWG2 guidelines advocate that any change in tumor size at the first 12-week assessment should be confirmed in a later scan, and in the context of clinical evidence, progression in a new nodal or visceral site is considered sufficient to indicate disease progression [16]. Recently updated RECIST 1.1 guidelines may help to streamline this process by reducing the number of target lesions required for measurement and changing nodal size criteria/measurement and progression standards. The new guidelines will still need to be assessed in light of PCWG2 criteria with regard to, for example, the appearance of bone scan flare (see below) [32].

**Bone Scans**

The radionuclide bone scan is a simple, noninvasive method for detecting bone metastases, especially osteoblastic metastases (predominant clinical presentation in advanced prostate cancer). Although bone scan is generally reserved for patients with elevated PSA (>10 ng/mL) [33], it may also be useful for 2% of newly diagnosed cases with features of small cell or neuroendocrine differentiation who

---

**Table 1. (Continued)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Suggested outcome measure (PCWG1)</th>
<th>Suggested outcome measure (PCWG2)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of life</td>
<td>Not addressed</td>
<td>Serial assessment required</td>
<td>Patient measurable</td>
<td>• Requires validated scales</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Qualitative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Defines clinically significant changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Bias in nonplacebo trials</td>
</tr>
<tr>
<td>Pain</td>
<td>Not addressed</td>
<td>Serial assessments of pain</td>
<td>Patient measurable</td>
<td>• Qualitative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>management</td>
<td></td>
<td>• CRPC is often pain free</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Pain may be unrelated to progression</td>
</tr>
<tr>
<td>Overall survival</td>
<td>Not included</td>
<td>Not included</td>
<td>• Accepted trial endpoint</td>
<td>• Time needed for efficacy of some agents to emerge may exceed survival in high-risk populations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Highlight advantages in patient populations with short expected survival</td>
<td>• Secondary treatments may also increase survival</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>Not included</td>
<td>See above (progression)</td>
<td>Highlight clinical benefit</td>
<td>Remains to be defined</td>
</tr>
<tr>
<td>Circulating tumor cells</td>
<td>Not included</td>
<td>Not included</td>
<td>Early detection (prior to PSA)</td>
<td>• Sensitivity questioned for widespread metastases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Not validated surrogate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Expensive</td>
</tr>
</tbody>
</table>

Abbreviations: CRPC, castration-resistant prostate cancer; PCWG, Prostate Cancer Clinical Trial Working Group; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.
have minimal PSA production [34, 35]. Bone scintigraphy predicts the risk of spinal cord compression, a major cause of morbidity in CRPC [36]. However, scintigraphy may lack sensitivity compared with magnetic resonance imaging (MRI) for early detection of spinal metastases [37].

Because tracer uptake usually decreases after chemotherapy, hormone therapy, or radiotherapy, radionuclide bone scanning has also been used to assess treatment response [33]. However, studies have failed to show a strong association between bone scan progression and overall survival [27]. One possible explanation is that bone scans performed shortly after treatment initiation may simply reflect the disease progression that led to trial enrollment and not treatment failure. In addition, osteoblast-mediated healing of pre-existing metastatic foci may give the false appearance of worsening disease (bone scan flare) in an otherwise responding patient, when in fact the opposite is occurring. Although it remains poorly quantified, bone scan flare usually occurs within the initial 3 to 6 months following a new therapy, but its duration remains unclear, suggesting that bone scans should not be performed for a minimum of 3 months after the start of treatment [27]. Further research in controlled trials is needed to quantify the duration of the bone scan flare phenomenon. PCWG2 guidelines suggest that when scan findings are suggestive of flare or where new lesions may represent trauma, results should be confirmed with additional confirmatory imaging techniques, such as MRI or fine-cut computed tomography, or repeat bone scanning 6 weeks after the initial scan [16].

**MARKERS OF BONE TURNOVER: URINARY N-TELopeptide AND BONE-SPECIFIC ALKALINE PHOSPHATASE**

Urinary N-telopeptide (NTx), a biochemical marker of bone collagen breakdown corresponding to osteoclast activity, is a recognized indicator of bone metastases. Although the clinical pathology of bone metastases in prostate cancer is overtly osteoblastic, an osteoclastic step is a critical prequel during the metastatic process [38, 39]. In one study, elevated NTx levels found in patients with a range of progressive solid cancers, including prostate cancer, correlated with the extent of bone metastasis, as confirmed by bone scans [40]. Of biochemical markers evaluated, NTx was the most predictive of bone metastases. NTx elevation could identify early bone metastasis after primary tumor removal, which would otherwise be undetectable by bone scanning, enabling earlier and more effective therapeutic intervention. Elevated NTx levels correlate with an increased risk of death, progression, and skeletal-related events in metastatic prostate cancer and other tumor types, thereby acting as a potential surrogate marker for treatment efficacy [22, 41–43]. In a recent study, elevated NTx levels were a strong independent predictive factor for decreased survival in CRPC patients treated with zoledronic acid [44]. Further analysis of the association between NTx decrease and survival in a multivariate analysis after accounting for all known prognostic factors is required. In addition, no association was observed between NTx and survival in CRPC treated with atrasentan [6], indicating that NTx as a surrogate marker for response remains unclear.

Bone-specific alkaline phosphatase (BAP) is a bone formation marker reflecting osteoblast activation. Elevated serum BAP correlates with the extent of bone metastatic involvement in patients with cancer and predicts skeletal complications in prostate cancer [40, 41, 45]. Increasing BAP levels at initiation of hormonal therapy signify a poor prognosis, with rapid progression to bone metastasis [46]. In a multivariate analysis of data from a randomized trial in metastatic prostate cancer, higher serum BAP levels were associated with shorter overall survival [47]. Alkaline phosphatase levels also independently predicted overall survival in docetaxel-treated patients and are a central component of pretreatment nomograms used in CRPC [22, 42]. The utility of BAP versus total alkaline phosphate levels alone, however, is unclear. Overall, this marker reflects the importance of the bone microenvironment in determining prognosis [42, 48].

The correlation between BAP and patient outcomes suggests that changes in serum BAP levels may alert to treatment failure and/or a need for more aggressive treatment. However, there is insufficient evidence that BAP or NTx provides additional predictive information beyond traditional risk factors. Although this justifies their exclusion from the most recent PCWG2 guidelines, bone turnover markers provide important information regarding effects on bone metastases and may hold future promise as surrogates for therapies specifically targeted to the bone microenvironment.

**Pain**

Bone pain is a classic indicator of metastatic prostate cancer and abrogation of pain may reflect response to therapy. In a large trial in men with advanced prostate cancer receiving docetaxel or mitoxantrone, pain responses were highly predictive surrogate indicators for survival [19, 49]. In a combined analysis of three phase III trials, the baseline pain interference score (assessing the impact of pain on daily activities and quality of life) was a statistically significant predictor of survival. In men with low (<17) or high (≥17) pain scores, median survival was 17.6 months (95% CI, 16.1 to 19.1 months) and 10.2 months (95% CI, 8.6 to 11.3 months; p < .001), respectively [50]. Pain was inversely as-
associated with likelihood of PSA decline, objective response, and time to bone progression (Table 1) [27, 50, 51]. Pain assessment requires the use of validated instruments and involves a high degree of subjectivity and bias in nonblinded studies. Prospective validation of pain response and time to progression as a surrogate in phase III trials is warranted but may serve as a measure of clinical benefit itself to warrant registrational strategies.

Circulating Tumor Cells
CTCs are now widely recognized as often present and detectable in men with CRPC. The association between baseline CTC number and clinical outcomes including survival in metastatic prostate cancer has been clearly demonstrated [52–55]. Recent prospective data have shown that among men with progressive CRPC, changes in CTC number after 4, 8, or 12 weeks of chemotherapy were more strongly predictive of survival than changes in PSA [55]. CTC count prior to initiating systemic chemotherapy has been demonstrated to be independently prognostic [52, 54, 56] and to be independently predictive of benefit from systemic chemotherapy [54], with predictive accuracy outperforming PSA decline at all time points. Finally, CTC response and progression may be useful for following patients receiving chemotherapy and to predict survival in addition to known prognostic factors [55]. Earlier this year, the FDA approved the CellSearch System (Veridex, LLC, Raritan, NJ) to identify and count CTCs for predicting overall survival in patients with metastatic breast, colorectal, or prostate cancer [52, 53]. One major issue with CTC count in CRPC is the low frequency of captured cells in the prechemotherapy setting, limiting its potential use as a biomarker and source of evaluable tumor tissue for correlative studies, even in the presence of bone metastases. In addition, because the optimal cut point for CTC response and formal demonstration of surrogacy is lacking for this biomarker, its current impact on patient management decisions is unclear. However, CTC changes may precede PSA decline, providing early evidence of clinical benefit in chemotherapy-treated metastatic CRPC [54]. Prospective credentialing of the CTC test is ongoing in multiple phase III studies.

Although CTC enumeration is the most developed assessment method, future assays of molecular markers within CTCs may also be predictive and/or surrogates for response. CTCs can already be assayed for AR gene amplification and EGFR receptor (EGFR) expression [57]. In addition, fusion proteins and chromosomal rearrangements (e.g., TMPRSS2-ERG rearrangements) or broad gene expression profiles can be evaluated in CTCs or disseminated tumor cells in bone marrow to elucidate mechanisms of disease progression and tumor heterogeneity or clonality [58–60]. Analysis of particular genes such as the tumor suppressor PTEN, and AR levels, by fluorescent in-situ hybridization analysis may also be studied in CTCs to demonstrate the heterogeneity of CRPC during progression [58]. In a proof-of-principle study, EGFR mutations within CTCs conferring resistance to EGFR inhibitors were associated with poor patient responses to anti-EGFR treatment for lung cancer [61]. Thus, along with decreased numbers, specific genetic events within CTCs may prove to be predictive. Given the difficulty in obtaining tissue for direct tumor biomarker analysis, CTCs may be a rich source of biomarkers to accelerate drug development, enrichment of patients most likely to benefit from a given targeted therapy, and classification of disease at the molecular level. Future efforts to improve the recovery of these cells, such as the microfluidic chamber, should advance this field considerably [62].

APPLICATION OF PCWG2 GUIDELINES TO A CASE EXAMPLE: SRS FAMILY KINASE INHIBITION
Aberrant src/SFK signaling has been implicated across multiple stages and models of prostate cancer, including progression to metastatic bone disease. Inhibition of src or LYN signaling results in decreased proliferation, invasion, and migration of prostate cancer cell lines in vitro and in vivo [63–66], suggesting that these proteins are a reasonable target for drug development [12, 67, 68]. src inhibitors with preclinical activity relevant to prostate cancer are undergoing clinical trials. Two key agents in this setting are AZD0530 and dasatinib, although several others are in developmental pipelines (e.g., XL999, SKI-606).

Dasatinib (BMS-354825, Sprycel; Bristol-Myers Squibb Company, New York) is an oral inhibitor of several oncogenic kinases, including SFKs and ABL, linked to multiple human malignancies and is approved for chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia after failure of prior therapy. In experimental studies, dasatinib inhibited SFK activity and downstream substrates, which were accompanied by a reduction in the proliferation of PC-3 human prostate cancer cells [69] and the adhesion, migration, and invasion of DU-145 human prostate cancer cells [63]. In orthotopic nude mouse models, dasatinib reduced tumor growth and lymph node involvement, suggesting that src and LYN activity impacts key functions needed for prostate tumor progression [70]. Dasatinib also inhibits the ephrin A Receptor kinase, EphA2, which has been implicated in the malignant transformation of prostate cancer cells [71, 72].

A single-arm phase II study of dasatinib monotherapy in patients with progressive CRPC is ongoing (NCT00385580). The primary endpoint is a composite of both conven-
tional and surrogate markers, defined as the proportion of patients achieving at least one of the following: confirmed PSA response (decrease in PSA value ≥50%, with confirmation); confirmed improved bone scan (disappearance of ≥1 lesion and no new lesions on radionuclide assessment, no new pain), or tumor response (prolonged stable disease [SD] or confirmed complete response [CR] or partial response [PR] in target lesions according to RECIST). Secondary endpoints also include changes in PSA kinetics, rates of PSA declines, reduction in NTx/BAP levels, and safety/tolerability. Only preliminary data have been reported, with efficacy measures not yet fully assessable using the PCWG2 guidelines in terms of delaying/preventing metastatic progression. Preliminary results showed a composite radiologic benefit rate of 13 (28%) of 47 patients, including 1 patient with a confirmed PSA response and 12 patients with SD. Disease control rate (CR + PR + SD) among RECIST-evaluable patients was 50% [13]. Dasatinib monotherapy improved PSA doubling time in 33 (77%) of 43 patients, although it should be emphasized that, in the absence of a control arm and given known natural variability, changes in PSA kinetics are difficult to interpret [16, 73]. Dasatinib treatment resulted in normalization of NTx levels in 52% of patients (irrespective of concurrent bisphosphonate use) and a decrease in BAP levels in 63% [13]. Data on PFS and bone scan progression remain premature but median duration of therapy was only 2.9 months (range 0–9 months). Currently, follow-up is too short to assess PFS, time to progression, and overall survival, preventing full interpretation according to PCWG2 guidelines. These results underscore the challenges facing phase II trials in identifying candidate agents for phase III.

To increase and prolong response to docetaxel in CRPC, a rationale exists for combined treatment with a SFK inhibitor, given the possible dual benefits of direct antitumor effects and osteoclast inhibition (i.e., targeting of bone metastases). A phase I/II study of docetaxel plus dasatinib in patients with CRPC has demonstrated the tolerability and lack of PK interactions with this combination [74], and a phase III study of docetaxel and prednisone with or without dasatinib is ongoing with overall survival as the primary endpoint (NCT00744497). Again, favorable effects on markers of bone metabolism have been observed, as have PSA declines; however, the lack of a control arm and the lack of information on duration of benefit with this combination make it difficult to discern the additive benefit of dasatinib to docetaxel in this setting [74]. These data emphasize a need to improve current measures of surrogacy so that randomized phase II studies can be conducted in men with CRPC that will provide meaningful and timely go/no go decisions prior to phase III.

**PREDICTING RESPONSE TO SRC KINASE INHIBITORS?**

Like other cancers, there is a trend toward individualizing patient treatment algorithms for prostate cancer. Efforts are under way to establish a “kinase signature” for src inhibition. In preclinical prostate cancer models, 10 genes not only were potential efficacy markers but also had reduced expression following dasatinib exposure. In particular, five biomarkers (AR, PSA, cytokertatin 5, urokinase-type plasminogen activator, and EphA2) correlated with sensitivity to dasatinib, which may assist with future patient stratification and monitoring [75]. Phospho-src may also be useful as a pharmacodynamic biomarker for dasatinib in prostate cancer [76]. When CRPC tumors were analyzed using genomic signatures for AR and src activity, src-predicted activity increased as AR activity decreased [77, 78]. In addition, when src activity was predicted to increase, so did the probability of response to dasatinib, as measured using an expression-based system [78]. Thus, given preclinical observations that SFKs can bypass AR activity, src inhibitors may be most effective in CRPC with low-level AR activity, or AR-null cancers.

**SUMMARY**

Surrogate markers provide the opportunity for improving patient selection, optimizing patient management, and identifying therapies that should be brought forward to definitive phase III testing. Strong surrogates can accelerate phase III testing by providing earlier valid endpoints to help design and interpret trials. The recent PCWG2 recommendations represent the state of the art with respect to patient disease states and measures of therapeutic impact in prostate cancer. These recommendations highlight the challenges involved in interpreting changes in serum PSA and stress that composite trial endpoints are more likely to accurately reflect efficacy than individual endpoints. However, it is inherent in the definition of a surrogate that each surrogate is dependent on the disease state and the mechanism of action of the drug in question, and a surrogate for one state or therapy cannot necessarily be extrapolated to other disease states or drugs. Matching surrogate biomarkers with the underlying biology and drivers of tumor growth should accelerate drug discovery efforts. Given the recent demonstration of a survival benefit with sipuleucel-T (Provenge; Dendreon, Seattle) autologous dendritic cell vaccination over placebo vaccination despite a lack of impact on surrogate measures (PFS, response rates) [30], there
is clearly a need to develop improved tools for assessing the benefits of novel therapies, such as immune-based therapies, in cancer.

A growing understanding of AR signaling and crosstalk has led to targeted agents with relevant mechanisms of action and proven efficacy/tolerability in other cancers to be evaluated in advanced prostate cancer. In addition to potential antitumor, antimetastatic, and bone-normalizing effects, src inhibitors such as dasatinib could restore sensitivity to androgen ablation or provide benefit to men with CRPC who have low AR activity [23]. Although the goal is to translate into a clinical benefit, the optimal method to assess impact on disease remains to be determined. Trial endpoints that account for a drug’s mechanism of action create the greatest potential for success.

Looking ahead, the approach proposed by the PCWG2 may result in strong surrogate markers for survival for phase II studies. Unfortunately, there are currently no validated surrogate markers for assessing early clinical benefit from systemic therapy in metastatic CRPC [48]. Future trials designed using the current guidelines should improve efficacy evaluation. Trials initiated prior to the PCWG2 guidelines should still yield agents warranting further clinical evaluation. For ongoing phase II trials with maturing data, in-depth analysis is required, and regardless of the primary endpoints used, investigators should be encouraged to discuss their findings in light of new guidelines. Making the go/no go decision to progress to phase III development has never been simple. The decision will become easier as our understanding of surrogate markers increases.

**REFERENCES**


