Clinical endpoints for drug development in prostate cancer

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Purpose of review
Overall survival remains the benchmark in phase III settings of novel agents in castration-resistant metastatic prostate cancer. This review highlights many of the current potential early measures of response and clinical benefit that are worthy of future study and validation in this disease.

Recent findings
The clinical evaluation of novel agents in advanced prostate cancer remains challenging for several reasons. Men with metastatic prostate cancer often have bone-only disease in which formal radiologic response and progression criteria may not apply. Declines in serum prostate-specific antigen levels may be modest surrogates of response to cytotoxic agents such as docetaxel, but have not been validated for agents with novel mechanisms of action, such as antiangiogenic, immunologic, or cytostatic drugs. Novel radiologic imaging techniques such as PET scans are not yet validated for use in monitoring or staging advanced prostate cancer. Measures of delay, control, and palliation of metastatic disease such as pain response, time to progression and progression-free survival, while appealing endpoints that may highlight the clinical benefit of novel agents, have been difficult to define rigorously and have not yet demonstrated adequate surrogacy for overall survival.

Summary
The measures of response highlighted in this review, if validated, may improve the current evaluation of novel agents in phase II settings and the potential accelerated approval of these agents.

Keywords
castration-resistant prostate cancer, chemotherapy, hormone-refractory metastatic prostate cancer, novel therapies, prostate-specific antigen, surrogate endpoints

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Introduction

In 2008 there are as yet no validated surrogate endpoints for the assessment of early clinical benefit from systemic therapy in metastatic castration-resistant prostate cancer (CRPC). The reasons for this include difficulty in objectively quantifying changes in bone scans and prostate-specific antigen (PSA) levels that are not always associated with clinically important or approvable endpoints such as overall survival or pain palliation. Response Evaluation Criteria in Solid Tumors (RECIST) criteria, which are used to determine radiographic response in most solid tumors, are not easily applicable to the most common radiographic site of metastasis in prostate cancer (bone). For rapid and successful development of novel agents, we need early measures of efficacy in phase II trials in CRPC that will provide an improvement in overall survival in phase III testing. The following is an overview of many of the standard and investigational clinical choices for monitoring response.

Endpoints in phase II and III trials in castration-resistant metastatic prostate cancer

The following is an outline of the different endpoints studied to evaluate response in phase II and III studies in metastatic CRPC (Table 1) [1,2•,3–8].

Prostate-specific antigen declines

The widespread use of PSA as a screening measure led to its incorporation as a biomarker of response to hormonal and cytotoxic agents in advanced or recurrent prostate cancer [9]. Initial studies were based on a collection of trials of marginally effective agents that did not demonstrate an overall survival advantage, and were essentially based on the prognostic value of PSA changes [3]. Using these data, the first PSA Working Group [3,4] published widely accepted criteria for a PSA partial response: a 50% decline in PSA from baseline, confirmed 4 weeks later, in those patients with sufficient levels of PSA (usually

Table 1 Summary of standard and investigational endpoints for clinical trials in castration-resistant prostate cancer (CRPC)

Endpoint	Trial/author	Pros	Cons
PSA decline	Petrylak [1,2•] Scher [3,4] Armstrong [5]	Easily measurable Widely available Time < 3 months Evidence to support use with cytotoxic therapy	Not validated with novel agents PSA can rise after start therapy in minority Threshold unclear Does not allow for unique mechanism of novel agents
OS	TAX 327 [6]	Accepted endpoint Could enrich studies for short expected survival (risk-adapted studies)	Length of time for treatment by novel agent Secondary treatments may modify overall survival hypothetically
PFS	Scher [3,4] Armstrong [5]	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 Censorship prevents current surrogate analyses
Pain	TAX 327 [5,6]	Direct patient measure	Qualitative thus requires validated scales Many men with CRPC are painfree Not validated Cannot be used as a marker by itself – many causes of pain independent of tumor progression
QOL	Tannock [6]	Direct patient measure	Qualitative thus requires validated scales/measure Defining clinically significant changes Bias is inherent in nonplacebo-controlled trials
RECIST	Scher [8]	Well defined criteria if measurable disease present	No target lesions in patients with increasing PSA and localized disease, or bone-only disease Not always measurable soft tissue disease in prostate cancer No correlation with clinical or PSA progression Important treatment effects are missed
CTCs	Moreno [7]	Early detection before PSA rise	Only approximately 50% of men have detectable levels even with widespread metastases Not validated as surrogate yet Expensive, performed in specialized labs only Quick turnaround necessary

PFS, progression free survival; OS, overall survival; QOL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; CTC, circulating tumor cell; PSA, prostate-specific antigen.

>20 ng/ml). This level of decline was strongly prognostic in studies of cytotoxic agents; however, surrogacy was not demonstrated.

The initial analysis of PSA declines as surrogates for overall survival was performed by Petrylak *et al.* [1,10] using data from the Southwest Oncology Group Protocol 99-16 (SWOG 99-16). In this study, men with metastatic CRPC were randomly assigned to either docetaxel/estramustine or mitoxantrone/prednisone treatment, with docetaxel/estramustine providing a 2–3 month overall survival benefit. PSA declines of 5–90% and PSA velocity at 1, 2 and 3 months were tested for surrogacy. The Group concluded that a 30% or greater PSA decline with cytotoxic chemotherapy fully captured the overall survival benefit seen in this trial (100% surrogacy) and thus this level of decline would be a reasonable surrogate for a phase II endpoint. This study, however, was retrospective and required prospective validation.

Armstrong and colleagues [2•] from the TAX 327 study group examined various degrees of PSA decline and pain response as surrogates for the survival benefit observed for docetaxel and prednisone. They showed that a 30% or greater PSA decline within 3 months of starting treatment also showed the greatest degree of surrogacy, but in this study accounted for about two-thirds of the overall survival benefit seen.

In summary, PSA declines are highly prognostic and an easy measure to evaluate response within a few months of initiation of chemotherapy, but no one cutpoint fully predicts for benefit in a population or individual patient. Since no therapy, other than docetaxel chemotherapy, has demonstrated a survival advantage in CRPC, PSA declines have an uncertain role in the evaluation of these agents with novel mechanisms of action. With advanced metastatic CRPC, PSA production may not be consistent in all cancer cells. Since targeted therapies may impact specific subsets of cancer cells, PSA changes may or may not reflect this biology. Therefore, we recommend recording changes in PSA levels in patients on phase II and III trials of novel agents, but caution using this endpoint as a sole means of determining efficacy.

Radiologic response

Using the RECIST criteria in trials of men with CRPC has several problems which were well illustrated in a study done by Scher and colleagues [3,5]. When RECIST criteria are applied to men with CRPC, less than half of patients have measurable target lesions greater than 2 cm in size. These lesions were mainly lymph nodes that are

not always present in recurrent or advanced prostate cancer. RECIST does not apply to localized or PSA-only recurrent prostate cancer. There are no criteria in RECIST for patients with 'flare' phenomena, when healing bone lesions after starting therapy may appear as worsening existing or even as new lesions [3,11]. To address this deficiency, current guidelines have been established to require confirmatory bone scans for new lesions seen on initial bone scans before stopping therapy that is otherwise continuing to benefit a patient [3].

Pain and quality of life improvements

Pain and other cancer-related symptoms can serve as useful markers of clinical benefit in patients with metastatic CRPC. Improvement in pain responses and duration led to the approval of mitoxantrone for men with CRPC. Two randomized controlled studies compared mitoxantrone/prednisone with prednisone therapy alone in patients with metastatic CRPC and demonstrated improved pain control and duration as well as better quality of life in favor of mitoxantrone [6]. One limiting feature with a pain control endpoint is that many patients with CRPC do not have pain yet have a relatively short expected survival, on the order of 1.5–2 years. Restricting the study of novel agents to men with CRPC and significant pain would limit accrual to clinical trials for this lethal disease, unless the agent was intended as a purely palliative therapy. Regarding quality of life, outcomes remain problematic given their subjectivity, lack of standardization, inherent biases in comparison with control arms, and the need to balance quantity of life improvements with quality of life improvements [12•].

Skeletal-related events

In certain circumstances, a novel clinical endpoint may be utilized that directly reflects the mechanism of action of the agent being tested. A good example of this is the approval of zoledronic acid for the prevention of skeletal related events despite no difference in overall survival [13]. In a multicenter randomized controlled trial, Saad *et al.* showed that the bisphosphonate zoledronic acid significantly decreased incidence of bone-related complications in patients with prostate cancer with osteoblastic bone lesions. Zoledronic acid also increased the time to first skeletal event and decreased bone pain compared with placebo. This endpoint thus represents a potential mechanism for approval of agents that target bone health rather than the tumor directly, but will likely need to improve on zoledronic acid as the standard comparator.

Progression-free survival and time to progression (time to event endpoints)

Scher *et al.* [14•] retrospectively explored the association between progression-free survival (PFS) and overall survival time in patients with CRPC treated with microtubule-targeted therapies. They looked at the association between radiographic PFS and PSA PFS with overall survival and these were adjusted for censoring. They found that the overall association between PFS and overall survival time was weak to moderate: 0.4 for radiographic PFS and 0.33 for PSA PFS (on a 0–1 scale with 1 indicating perfect surrogacy). The association between radiographic PFS and overall survival was weakest early in the follow-up process, whereas the PSA association was weakest when the PFS-related event (PSA progression, death, or censoring) occurred after 6 months from the start of treatment. They concluded that current measures of PFS for men with CRPC are not strong surrogates for overall survival. Factors that reduce this association include interval censoring of progression data and the discontinuation of therapy early in the follow up due to imaging changes that may not reflect true failure of the treatment. For radiographic PFS, a second confirmatory bone scan may increase the surrogate value of this endpoint.

Armstrong *et al.* [2•] evaluated various definitions of progression in the TAX 327 trial for postprogression survival and the benefit associated with continuing or stopping chemotherapy. They found that the more criteria that were met for progression, the lower the postprogression survival. For example, men who had progression by only one criterion (PSA, pain or tumor) lived a median of 15–17 months after progression on docetaxel. Men who progressed by two criteria lived a median of 10–14 months after progression, while those who met all three criteria had a median postprogression survival of only 7.8 months. A survival advantage to continuing chemotherapy was suggested for those men who had pain progression only. These data indicate that composite PFS definitions may be more clinically useful, and that if pain is included in the PFS definition, it should be combined with other measures of clinical progression, such as PSA or tumor progression.

Recent studies have used a composite endpoint of PFS which included tumor progression, skeletal events and symptomatic progression (i.e. pain), but not PSA changes as in the Satraplatin and Prednisone Against Refractory Cancer (SPARC) trial by Sternberg *et al.* [15]. Satraplatin, a novel oral platinum compound, was evaluated in this multinational randomized double-blind study comparing satraplatin and prednisone to prednisone and placebo in CRPC patients who failed prior chemotherapy. In this analysis, PFS was the primary endpoint, defined as a composite endpoint of radiologic progression, symptomatic progression, skeletal events or death. Satraplatin was associated with reduction in risk of PFS and decreased pain progression. Also noted was significant improvement in pain, tumor and PSA response rates [16]. Median survival, however, was not statistically different

and consequently the differences in median PFS and pain have not yet been validated as surrogates for overall survival in this setting.

Overall survival: TAX 327 data

Currently, overall survival remains the benchmark for the evaluation of novel agents in trials of men with CRPC. Given the problems associated with PSA declines, tumor responses, pain improvements, and lack of data on other radiologic or blood-based biomarkers, these endpoints cannot currently be recommended as approvable endpoints for agents whose intent is not purely palliative. The TAX 327 primary endpoint was overall survival, with secondary endpoints including pain, PSA levels, and quality of life [6]. Median overall survival in TAX 327 was improved by 2–3 months in the every 3-week docetaxel arm versus the every 3-week mitoxantrone arm (18.9 versus 16.5 months, hazard ratio 0.76, $P = 0.009$). The every 3-week regimen also showed statistically significant improvements in pain control, quality of life, and PSA level. Currently there are a number of ongoing phase III trials with docetaxel and prednisone backbone as a comparator; overall survival is the primary endpoint for these studies. Until a reasonable surrogate can be identified in these trials, overall survival will continue to be used. Given the difficulty in validating a surrogate and the dependence of a surrogate on the mechanism of action of the therapy, it is unlikely that a novel surrogate will replace overall survival in the near future.

Novel biomarkers

New biomarkers for disease response in CRPC could be valuable for several reasons. As a complement to PSA, additional biomarkers may identify other functional pathways for CRPC. Like PSA, other biomarkers could be monitored serially and frequently in patients, allowing for trends over time to be used as well as baseline values. One novel surrogate being investigated in patients with CRPC is circulating tumor cells (CTCs). CTCs have demonstrated strong prognostic significance and predictive value for response to therapy [17]. A recent study by Moreno *et al.* [7] used CTCs in CRPC patients undergoing cytotoxic chemotherapy to predict outcome and monitor ongoing treatment response. This study found that patients with decreasing levels of CTCs after starting therapy had increased overall survival compared with those who did not have reduction in CTCs: 20 versus 9.3 months. CTCs were not detectable in about half the study patients even though they had widespread metastases. Given that many patients with CRPC do not have detectable levels of CTCs, it remains to be seen how reliable a surrogate this test will be and prospective validation in a trial with a survival advantage to therapy is needed. There are current plans for exactly this type of analysis in a second-line study of the novel adrenal androgen lowering agent abiraterone acetate and prednisone versus prednisone alone.

Assessment using imaging modalities

Bone scans are generally used in patients with PSA greater than 10 ng/ml to assess risk of distant spread. Lesions may not be visible in early disease, however, if no osteoblastic response is present. There may also be false positive findings associated with degenerative disease or previous trauma. Also there may be 'flare' phenomena when uptake increases after chemotherapy during bone remodeling [14•].

F-18 fluorodeoxyglucose (FDG) PET scan has been shown to be better than both bone scan and computed tomography scan for discerning between actual metastasis and healing bone [18]. FDG does not do as well in distinguishing tumors from inflammation [19] and newer tracers are being investigated to this end. Some of these include methionine as well as ^{11}C acetate and ^{11}C choline. ^{18}F fluorodihydrotestosterone has also recently been studied to assess androgen receptors [18].

MRI and magnetic resonance spectroscopic imaging (MRSI) data have shown that tumor detection is dependent on tumor grade, with tumor detection at 90% for Gleason score 8–9 [20]. There was a suggestion in this study of correlation between metabolic abnormality detected on MRSI and the aggressiveness of the cancer. Studies are underway to look at findings on MRI and MRSI and their correlation with tumor pathology and a variety of molecular markers including Ki-67, PTEN, phosphorylated AKT and Bcl-2 [18].

Tissue and pathologic endpoints

The spectrum of prostate cancer progression together with our increasing understanding of tumor biology and of novel agents directs us to study tissue endpoints that address mechanism of action and pathologic effects. A number of studies are being done with novel agents in the preprostatectomy setting. For example, in a preprostatectomy rapamycin study (Table 2 [21–33]), the primary endpoint is inhibition of the downstream mammalian target of rapamycin (mTOR) targets S6 kinase phosphorylation and 4EBP1 activation, with secondary endpoints being changes in proliferation and apoptosis. For our ongoing RAD001 phase II study in CRPC, induction of apoptosis (TUNEL) and reduction in proliferation in bone biopsies are pathologic endpoints, with the intent to correlate these with PTEN loss or Akt activation and clinical TTP. Each trial is uniquely geared to the mechanism of action of the drug (mTOR inhibition) and the clinical state. Preprostatectomy models may not, however, reflect the biology of progressive CRPC. Also these tissue biomarkers are not yet validated surrogates of clinical

Table 2 Studies using novel agents in the preprostatectomy setting

Trial/PI	Prostate cancer setting	Local treatment	Number	Phase	Regimen	Locations
Thomas [21]	High risk localized	RP	40	I/II	Temsirolimus	MD Anderson/ UCLA/Fox Chase
Amato [22]	Intermediate to high risk	RP	40	II	Cetuximab + docetaxel versus cetuximab	MHS
Chi [23]	Localized	RP	45	II	OGX-011	UBC
Trump [24]	Localized	RP	80	II	Calcitriol + dexamethasone	RPCI
Febbo [25]	Localized	RP		PD	Imatinib	DFCI
Carducci/ Armstrong [26]	Intermediate risk	RP	42	PD	Rapamycin (sirolimus)	JHM/UM/Duke
Lerut [27]	Localized	RP	15	PD	RAD001	Leuven, Belgium
George	Intermediate to high risk localized	RP	30	Pilot	Sunitinib	Duke
Lerut/Carducci [27,28]	Localized	RP	64	PD	Celecoxib	Johns Hopkins
Fong [29]	Any localized	RP	28	Pilot	GM-CSF	UCSF
Bergan [30]	Localized	RP	88	I/II	Genistein	RLCC
Kadmon [31]	Localized	RP	36	I	RTVP-1 gene therapy	Baylor
Oh [32]	High risk	RP	42	II	Docetaxel + bevacizumab	DFCI/BIDMC/Duke
Eastham [33] CALGB 90203	High risk, localized	RP	700	III	Docetaxel + estramustine	MSKCC

PI, principal investigator; RP, radical prostatectomy; UCLA, University of California Los Angeles; MHS, Methodist Hospital System, Texas; OGX-011, Oncogenex-011; UBC, University of British Columbia; RPCI, Roswell Park Cancer Institute; PD, pharmodynamic; DFCI, Dana Farber Cancer Institute; JHM, Johns Hopkins Medicine; UM, University of Michigan; RAD001, everolimus; GM-CSF, granulocyte macrophage colony stimulating factor; UCSF, University of California, San Francisco; RLCC, Robert H. Lurie Cancer Center; RTVP, related to testes-specific, vespid, and pathogenesis protein 1; BIDMC, Beth Israel Deaconess Medical Center; CALGB, Cancer and Leukemia Group B; MSKCC, Memorial Sloan Kettering Cancer Center.

benefit. Many of these biomarkers are sensitive to collection conditions (ischemic time, processing, freezing, manipulation, etc.) that make them difficult to evaluate, and the yield on bone biopsies in CRPC has been fairly low in the past. At Duke, we are trying to improve on this yield using computed tomography-guided pelvic bone biopsies and a dedicated radiology team that can improve on these techniques and number of core biopsies over time that can be used for genomic and proteomic measures.

Conclusion

In summary, the only validated phase III endpoint in advanced prostate cancer, particularly CRPC, is overall survival. Other measures of palliation and or clinical benefit, such as prevention of fracture, may be approvable in select scenarios depending on the trial design and drug mechanism of action. In phase II trials, however, it remains a challenge to select the ideal intermediate endpoint to gauge the efficacy of novel agents. The lack of proven surrogates, the heterogeneity of PFS definitions, the unknown effects of novel agents on PSA production, and the variability in patient-reported outcomes make many of these endpoints problematic. Current efforts to standardize case-report forms, reporting of trial results, and measures of response and progression will improve our ability to identify an ideal surrogate that may be used in phase II studies. Until that time, endpoints such as composite PFS definitions and rates of 3-month PSA declines (>30 or >50%) are reasonable but fallible measures of early activity and their use should intrinsically be linked to drug mechanism of action.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 341–342).

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