Eligibility and Response Guidelines for Phase II Clinical Trials in Androgen-Independent Prostate Cancer: Recommendations From the Prostate-Specific Antigen Working Group

By Glenn J. Bubley, Michael Carducci, William Dahut, Nancy Dawson, Danai Daliani, Mario Eisenberger, William D. Figg, Boris Freidlin, Susan Halabi, Gary Hudes, Maha Hussain, Richard Kaplan, Charles Myers, William Oh, Daniel P. Petrylak, Eddie Reed, Bruce Roth, Oliver Sartor, Howard Scher, Jonathan Simons, Vickie Sinibaldi, Eric J. Small, Matthew R. Smith, Donald L. Trump, Robin Vollmer, and George Wilding

Purpose: **Prostate-specific antigen (PSA) is a glycoprotein that is found almost exclusively in normal and neoplastic prostate cells. For patients with metastatic disease, changes in PSA will often antedate changes in bone scan. Furthermore, many but not all investigators have observed an association between a decline in PSA levels of 50% or greater and survival. Since the majority of phase II clinical trials for patients with androgen-independent prostate cancer (AIPC) have used PSA as a marker, we believed it was important for investigators to agree on definitions and values for a minimum set of parameters for eligibility and PSA declines and to develop a common approach to outcome analysis and reporting. We held a consensus conference with 26 leading investigators in the field of AIPC to define these parameters.**

Result: **We defined four patient groups: (1) progressive measurable disease, (2) progressive bone metastasis, (3) stable metastases and a rising PSA, and (4) rising PSA and no other evidence of metastatic disease. The purpose of determining the number of patients whose PSA level drops in a phase II trial of AIPC is to guide the selection of agents for further testing and phase III trials. We propose that investigators report at a minimum a PSA decline of at least 50% and this must be confirmed by a second PSA value 4 or more weeks later. Patients may not demonstrate clinical or radiographic evidence of disease progression during this time period. Some investigators may want to report additional measures of PSA changes (ie, 75% decline, 90% decline). Response duration and the time to PSA progression may also be important clinical end point.**

Conclusion: **Through this consensus conference, we believe we have developed practical guidelines for using PSA as a measurement of outcome. Furthermore, the use of common standards is important as we determine which agents should progress to randomized trials which will use survival as an end point.**

J Clin Oncol 17:3461-3467. 1999 by American Society of Clinical Oncology.

PROSTATE CANCER IS THE most commonly diagnosed malignancy among males in the U.S. and the second leading cause of cancer-related mortality. It is estimated that 39,000 men will die of prostate cancer in 1999.[1] Androgen ablation has been the cornerstone for the treatment of metastatic disease for more than 50 years,[2] but ultimately, almost all patients with distant metastasis will develop androgen-independent cancer and succumb to their disease. In addition, no therapeutic regimen has been shown to prolong survival in this setting.[3] The difficulties in determining the activity of new agents in androgen-independent prostate cancer (AIPC) are well documented (especially the slow resolution of bone lesions on bone scan). Most patients have disease limited to the bone, which is notoriously difficult to assess for response, with a small subset having soft tissue lesions. To limit trials to only patients with bidimensionally measurable disease would eliminate 70% to 80% of patients who would otherwise be eligible.[4] Lack of consensus on response criteria further complicates the evaluation of new treatments. A review of recently completed trials suggest that, even within one cooperative group, there is a wide variation in both the eligibility and response criteria used (N. Dawson, personal communication, February, 1999). These differences can impede the development of new agents (or regimens) and hinder the comparison between therapies.

From the Beth Israel Deaconess Medical Center, Dana Farber Cancer Center, and Massachusetts General Hospital, Boston, MA; Johns Hopkins University, Baltimore, MD, National Cancer Institute, Bethesda, MD, University of Maryland, Baltimore, MD, MD Anderson Cancer Center, Houston, TX, Duke University, Durham, NC, Fox Chase Cancer Center, Philadelphia, PA, Wayne State University, Detroit, MI, University of Virginia, Charlottesville, VA, Columbia University, New York, NY, Vanderbilt University, Louisiana State Medical Center, New Orleans, LA, Memorial Sloan Kettering Cancer Center, New York, NY, University of California at San Francisco, San Francisco, CA, Massachusetts General Hospital, Boston, MA, University of Pittsburgh, Pittsburgh, PA, and University of Wisconsin, Madison, WI.

Submitted April 19, 1999; accepted August 3, 1999.

Address reprint requests to William D. Figg, PharmD, Bldg 10, Room 5A01, Medicine Branch, National Cancer Institute, 9000 Rockville Pike, Bethesda, MD 20892; email wdfigg@helix.nih.gov.

0732-183X/99/1711-3461

Prostate-specific antigen (PSA) is a 34 kD glycoprotein that is found almost exclusively in normal and neoplastic prostate cells and seminal fluid.[5-8] Changes in PSA will often antedate changes on bone scan, and its use could theoretically permit new agents to be screened more rapidly for activity.[9-11] In 1989, Ferro et al[12] were the first to report PSA changes as an indicator of response in patients enrolled onto a trial for AIPC. Since then, the majority of phase II trials have used PSA as a marker.[13-15] However, some of the data currently available suggests that serum PSA cannot serve as a reliable surrogate end point.[14-17] Indeed, clinical experience has provided some settings in which PSA changes and "hard" end points, such as survival, were demonstrated not to correspond.[11,18] The use of PSA as a surrogate for benefit would require specific validation for the clinical setting and agents under investigation.

Published data lend support to the assumption that, for many agents, a decline in serum PSA may be a useful indicator of outcome in AIPC. This has been put forward by several groups as a potential outcome measure for survival in patients with AIPC.[14,17,19] Approximately 95% of patients with advanced metastatic cancer of the prostate have an elevated PSA.[4] Several investigators have attempted to correlate a decrease in PSA with clinical benefit and survival.[14-17,19,20] Most have noted that a posttherapy decline of 50% has been associated with a prolonged survival. Kelly et al[16] reported a statistically significant survival advantage in 110 patients if they had a posttherapy decline in PSA of 50% as opposed to those who did not (8.6 months v >25 months, respectively). Likewise, Smith et al[14] reported a significant increase in survival if the PSA decreased by 50% or greater at 8 weeks (median survival from a landmark analysis was 91 weeks in patients with a 50% or greater decrease v 38 weeks in those without this decrease). More recently, Scher et al[17] reported a multivariate analysis in which a posttherapy decline in PSA level of 50% achieved at both 8 and 12 weeks was a statistically significant factor associated with survival.

For the purpose of this discussion, we assume that guidelines can be established under which serum PSA can play a valuable role in pilot studies of new therapeutic approaches in androgen-independent disease purely as a tool for determining which approaches warrant selection for more definitive testing. The only underlying assumptions are that observed major decreases in PSA in association with a new treatment imply some biologic effect that encourages further evaluation and that lack of effect on an increasing PSA is likely to indicate an approach of little interest (unless preclinical testing has suggested the likelihood of a confounding effect on PSA gene expression, synthesis, or release). Used in this way, no assumption or claims of clinical benefit can or should be made; however, screening of new therapies could proceed much more quickly, and a larger number of patients would have the opportunity to participate in clinical research.

To use PSA most effectively, investigators must agree on definitions and values for a minimal set of parameters such as eligibility criteria, criteria for PSA response, and approach to outcome analysis and reporting. For many of these criteria, existing data does not permit an unequivocal determination of the "right" approach, but use of serum PSA for the limited purpose does not require that we begin with validated surrogacy data. All that is required is that investigators agree to use some standardized criteria, which can and should be updated as better data become available. In addition, these criteria for PSA response may require future validation.

Standardization of Terms

Unfortunately, even among investigators who have reported a decline in serum PSA as an end point, there is no consistency in how a PSA decline is measured and reported. Moreover, divergent criteria for treatment eligibility have been used. Trials have required different minimum PSA values and different criteria for biochemical progression after a previous treatment. In fact, a survey published in 1998 reported that among 35 leading investigators in the field, the response duration for a hypothetical patient varied by as much as 77 days (range, 49 to 126 days) because of differences in the calculation of response.[21] These data emphasize the need to standardize eligibility and response criteria to advance the field and develop new therapies.

EFFECT OF DRUGS ON PSA EXPRESSION

It is important to recognize that some agents may modulate PSA (either up- or downregulation) independent of their effect on cell growth.[22] The majority of those agents identified to date are not conventional cytotoxic agents. It is also important to emphasize that the models currently used to evaluate these changes have not been validated. Nonetheless, we would recommend that attempts be made to prospectively evaluate the effects of novel anticancer agents on PSA as an aid to interpreting clinical studies using PSA as an end point. For example, a phase II clinical trial in patients with AIPC was conducted using carboxyamido-triazole inhibitor, an agent that had been shown to downregulate the expression of PSA.[18,23] Therefore, the trial was limited to those with measurable soft tissue lesions. A large percent of patients were found to have decreases in their PSA, but their soft tissue lesions continued to grow, as demonstrated by serial radiographic studies.[18] These data emphasize the importance of understanding the effect of new agents on PSA expression.

RECOMMENDATIONS FOR ELIGIBILITY CRITERIA

For the purpose of this discussion, we have defined four groups of patients: 1) progressive measurable disease, 2) progressive bone metastasis, 3) stable metastases and an increasing PSA, and 4) increasing PSA and no other evidence of metastatic disease. Although performance status, weight change, and pain may be valid eligibility and response criteria for some clinical studies, they are not addressed in this manuscript.

Progressive Disease

Patients who are entered onto clinical trials of AIPC must have demonstrated evidence of progressive disease. Patients may have progressive measurable disease, worsening disease on bone scan, or an increasing PSA (as defined below).

Progressive measurable disease. Progressive measurable disease (changes in size of lymph nodes or parenchymal masses on physical examination or x-rays), regardless of changes in PSA, bone scan, or performance status, is adequate for protocol eligibility using conventional solid tumor criteria. Approximately 20% of patients with radiographic evidence of disease will have measurable soft tissue disease. In addition to PSA criteria, these patients may be evaluated using more traditional phase II criteria. For agents that seem to be promising based on PSA criteria, it may make sense to accrue additional patients with measurable disease to increase the understanding of the drug's activity.

Bone scan progression. Most investigators believe that a worsening bone scan is adequate evidence of progressive disease, regardless of changes in PSA. However, it is well known that bone scans may worsen ("flare") with the initiation of hormonal ablation and even chemotherapy.[24] This is manifested by dramatic serologic and clinical improvement at the same time a bone scan shows more intense lesions and occasionally even new lesions. Bone scans that worsen because of hormonal ablation or chemotherapy generally occur at the commencement of treatment and have not been difficult to detect clinically.

Patients who do not fit into this clinical scenario may have bone scans that demonstrate larger lesions, new lesions, or a combination of larger lesions and new lesions. Changes in the intensity or the size of a lesion may be difficult to interpret. Thus, we would suggest that at least one new lesion be evident before placing a patient onto a clinical trial based on progression in bone scan alone. In those patients entered onto clinical trials on the basis of nonmeasurable but assessable disease progression and who will subsequently be observed with PSA as an end point, the PSA level at trial entry should be greater than or equal to 5 ng/mL.

PSA progression. An increasing PSA, in some patients, may be the only evidence of progressive disease. Investigators have defined PSA progression in a variety of different ways, with variability concerning the amount of increase, number of required consecutive increasing values, and the time interval between the values. There is a theoretical conflict between easing requirements to allow more patients on phase II trials and using more stringent criteria for better accuracy in selecting which drug will undergo phase III testing. There are no randomized data that one can use to define PSA progression, so all criteria are somewhat arbitrary.

In those patients entering onto a clinical trial and having PSA progression as the only evidence of progressive disease, we suggest that two consecutive increases in PSA be documented over a previous reference value (see Fig 1). The first increase in PSA (no. 2) should occur a minimum of 1 week from the reference value. This increase in PSA should be confirmed (no. 3A). It is recognized that PSA fluctuations are such that the confirmatory PSA value (no. 3B) might be less than the previous value. In these cases, the patient would still be eligible provided the next PSA (no. 4) was found to be greater than the second PSA (no. 2 in the above sequence). We believe that a patient whose only evidence of progressive disease is an increasing PSA should have a value of at least 5 ng/mL before entering onto a clinical trial.

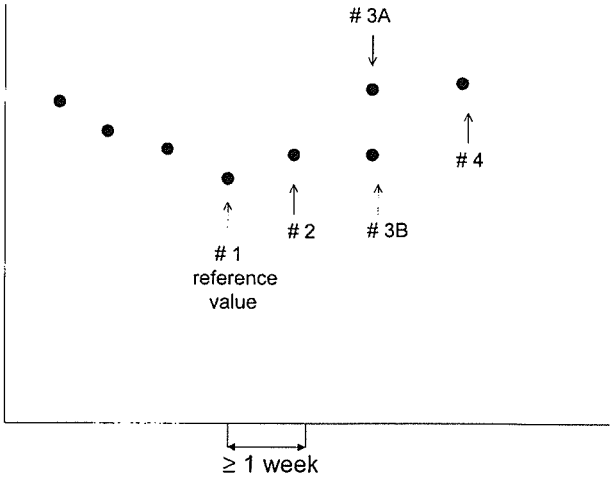

Fig 1. For defining eligibility, the reference value (no. 1) is the last PSA level before a sequence of increases. The interval between the reference value and time point no. 2 must be a minimum of 1 week. If the PSA at time point no. 3 (value no. 3A) is greater than at time point no. 2, then the requirement for a sequence of three increases has been met. If the third value is not greater than value no. 2, but value no. 4 is, then increasing PSA has been confirmed, and the patient can be eligible. In all cases, value no. 3A or no. 4 must be greater than or equal to 5 ng/mL.

Unfortunately, at lower values it is much more difficult to interpret changes in PSA. We believe this is problematic and, thus, a minimum PSA level is required.

Antiandrogen withdrawal. There is evidence that at least 20% of AIPC patients will have clinical and PSA responses by stopping their antiandrogen treatment.[3] Therefore, to standardize results, all patients need to demonstrate continued elevation of their PSA 4 to 6 weeks after the cessation of their antiandrogen treatment. The length of time is dependent on the half-life of the agent used. Four weeks is sufficient after flutamide withdrawal, and 6 weeks is required for other agents commercially available at this time.

Testosterone levels/suppression. To standardize this population as much as possible, all patients without surgical castration should have a serum testosterone level less than 50 ng/dL. There is no need to document a serum testosterone in patients having a prior surgical castration. In addition, patients should continue primary androgen suppression if they have not undergone surgical castration. The data for continuing androgen suppression are not definitive, but again, the intention is to make the patient populations from each trial as comparable as possible.

REPORTING TRIAL OUTCOMES

Posttherapy PSA Changes

The purpose of determining the number of patients whose PSA decreases in a phase II trial of AIPC is to guide the selection of agents for further testing and phase III trials. There have been attempts to determine if a posttherapy decline in PSA is of prognostic significance.[14-17,19] Many, but not all investigators have observed an association in uncontrolled trials between a decline in PSA levels of 50% or greater and survival.[11] There is also considerable controversy about the timing of the determination of the PSA level and the determination of the length of the response. The goal of the criteria herein proposed is quite focused to not use decline in PSA as a surrogate marker for survival but, instead, to use it as an outcome measure to guide the development of further trials, generally randomized. Thus, it is acceptable that these criteria are necessarily arbitrary. We propose that investigators should report, at minimum, a PSA decline of at least 50%, which must be confirmed by a second PSA value 4 or more weeks later. The reference PSA for these declines should be a PSA measured within 2 weeks before starting therapy. Patients may not demonstrate clinical or radiographic evidence of disease progression during this time period. Some investigators may want to report additional measures of PSA changes (ie, 75% decline and 90% decline).

For the purpose of defining duration of biochemical decline in PSA, we suggest defining two points on a time course, time to 50% increase from PSA nadir (PSA response duration) and time to first consistent PSA increase (ie, time to inflection or time to positive slope; see Fig 2). The PSA response duration should commence on the date of the first 50% decline in PSA. The response duration ends when the PSA value increases by 50% above the nadir, provided that the increase is at least 5 ng/mL (or back to the baseline). All PSA responses and progressions should be confirmed by a second determination.

The time from initial 50% decline until the time at which the PSA begins to consistently increase (the inflection point) is also of interest to investigators. For an individual patient, this inflection point would be defined retrospectively. We emphasize that clear radiographic or clinical evidence of disease progression would constitute evidence of progression regardless of changes in PSA.

Objective Response

Patients with measurable soft tissue disease may also meet traditional guidelines for tumor response. We believe that this should also be noted and included in any description of a clinical trial.

PSA Normalization

We strongly discourage the term "PSA complete response." There is no compelling evidence that patients

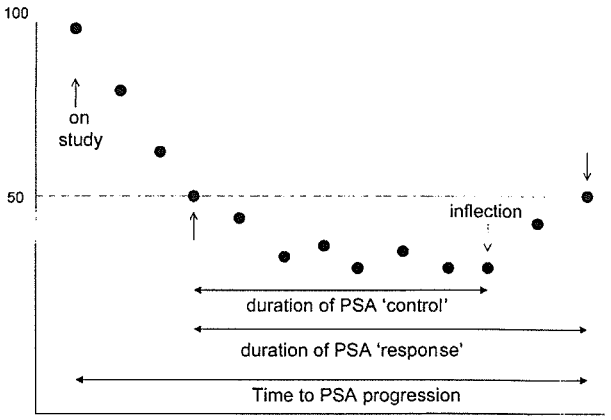

Fig 2. The duration of both PSA-based reporting end points are measured from the first time point at which the PSA has declined by at least 50% (which must eventually be confirmed by a second value). The duration of PSA response is the time until PSA has increased back to 50% of the original on-study value. However, in many cases, it will be possible (in retrospect) to identify an inflection point, the point at which PSA began what became a continuous increase. Some investigators feel that this may be considered the point at which disease control could be assumed to be lost. Thus, the duration of PSA control may be also be reported. Others prefer the time to PSA progression, which is defined as the time at which therapy started and ends when the PSA increases by 50% above the nadir.

whose PSA has normalized have a different long-term outcome than patients whose PSAs have declined by 50%. However, investigators may wish to report the number of patients achieving a PSA of less than 0.2 ng/mL.

DEFINING PROGRESSIVE DISEASE

Progressive Measurable Disease

Progressive measurable disease (changes in size of lymph nodes or parenchymal masses on physical examination or x-rays) is evidence of disease progression, regardless of changes in PSA, bone scan, or performance status.

Bone Scan Progression

Most investigators believe that a worsening bone scan is adequate evidence of progressive disease, regardless of changes in PSA. If there is strong evidence that a bone scan change is not indicative of progressive disease, then this should be noted and the patient continued on trial. Changes in the intensity or the size of a lesion may be difficult to interpret. Thus, we suggest that, if there is no evidence of flare, one or more new lesions are required to identify disease progression.[25]

PSA Progression

An increasing PSA may be the only marker of presumed progressive disease. In patients whose PSA has not decreased, progressive disease is a 25% increase over the baseline (on-study) and an increase in the absolute-value PSA level by at least 5 ng/mL, which is confirmed by a second value. In patients whose PSA has decreased but has not reached response criteria, progressive disease would be considered to have occurred when PSA increases 25% over the nadir, provided that the increase is a minimum of 5 ng/mL and is confirmed.

There are some trials in which investigators may wish to administer at least two cycles of therapy before removing patients from the study because of PSA progression. This is especially true for cytostatic agents that may require a period of time before treatment effect.

Time to PSA Progression

In the absence of evidence of clinical progression, the time to PSA progression is an appropriate outcome to report (especially for noncytotoxic agents). PSA progression may occur before clinical progression. The start of the time to PSA progression is the day treatment is initiated (time to progression as shown in Fig 2). If at least a 50% decline in PSA has been achieved, the end date is the time the PSA has increased 50% above the nadir at a minimum of 5 ng/mL (this is the same as the parameter for PSA response). For patients without a PSA decrease of this magnitude (or no decrease in PSA), the end point for progression will be calculated at the time a 25% increase in PSA has been achieved (see above). All end dates require a confirmatory PSA.

Stable Disease

The category of "stable disease" is controversial. There is no need to define or report stable disease as a category because the same information is contained in a more robust way within the definitions of time to PSA progression. The term stable disease may be used in the clinical situation as an interim classification of patients on an ongoing trial; however, this term should not be used when reporting an analysis of the data.

DESIGN, ANALYSIS, AND REPORTING

In general, multi-institutional phase II trials are preferred and encouraged because they tend to be less prone to extremes of patient selection bias and also serve better to test the "real world" feasibility of the therapy (facilitating the transition to phase III trials). For all phase II trials, primary analysis and reporting should be done in a fashion consistent with an intent-to-treat approach, treated patients should not be excluded from the analysis for disease progression or toxicity before an arbitrary time point, such as one or two cycles of therapy. The only exclusions should be patients who never started therapy or who died of an unrelated cause before initial evaluation. However, it is acknowledged that some investigators feel that adequate trials of cytostatic agents may require considerable periods of exposure before treatment effects may be observed. In such cases, the treatment protocol should include a prospective definition of an adequate trial, and a secondary analysis may be reported that is based on a denominator of adequately treated patients.

For all phase II trials, there should be a prospective identified, explicit, response rate of interest (or a time to PSA progression of interest, or both) and a (one- or two-stage) statistical design that explains the alpha and beta errors of the design. If the study includes different cohorts of patients (PSA only, PSA plus assessable disease or symptoms, or PSA plus measurable disease), it may be appropriate to have separate outcome parameters for these cohorts. Some patients will have AIPC yet have no evidence of disease on physical exam, bone scan, or computed tomography scan. These patients, when included in these trials, should be distinguished separately in the report from patients who have measurable or assessable evidence of disease. It is also recognized that prior treatment for patients with AIPC may influence subsequent response. For that reason, in the reporting of data, patients should be categorized by the number and type of hormonal and nonhormonal treatments previously administered.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.