

Eligibility and Outcomes Reporting Guidelines for Clinical Trials for Patients in the State of a Rising Prostate-Specific Antigen: Recommendations From the Prostate-Specific Antigen Working Group

Howard I. Scher, Mario Eisenberger, Anthony V. D'Amico, Susan Halabi, Eric J. Small, Michael Morris, Michael W. Kattan, Mack Roach, Philip Kantoff, Kenneth J. Pienta, Michael A. Carducci, David Agus, Susan F. Slovin, Glenn Heller, William Kevin Kelly, Paul H. Lange, Daniel Petrylak, William Berg, Celestra Higano, George Wilding, Judd W. Moul, Alan N. Partin, Christopher Logothetis, and Howard R. Soule

From the Memorial Sloan-Kettering Cancer Center; Columbia Presbyterian Medical Center, New York, NY; Brigham and Women's Hospital; Dana-Farber Cancer Institute, Boston, MA; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; University of California San Francisco, San Francisco; Prostate Cancer Center, Cedars-Sinai, Los Angeles; the Prostate Cancer Foundation (CaP CURE), Santa Monica, CA; Duke University, Durham, NC; University of Michigan, Ann Arbor, MI; University of Washington, Seattle, WA; Aventis Pharmaceuticals, Bridgewater, NJ; University of Wisconsin Comprehensive Cancer Center, Madison, WI; Uniformed Services University, Rockville; The Johns Hopkins Hospital, Baltimore, MD; and the University of Texas M.D. Anderson Cancer Center, Houston, TX. (Additional participants are listed in Appendix B.)

Submitted July 14, 2003; accepted November 14, 2003.

Supported by a Memorial Sloan-Kettering Cancer Center Specialized Program of Research Excellence grant in prostate cancer CA05826, the Prostate Cancer Foundation (CaP CURE), and the PepsiCo Foundation.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Howard I. Scher, MD, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021; e-mail: scherh@mskcc.org.

© 2004 by American Society of Clinical Oncology

0732-183X/04/2203-537/\$20.00

DOI: 10.1200/JCO.2004.07.099

A B S T R A C T

Purpose

To define methodology to show clinical benefit for patients in the state of a rising prostate-specific antigen (PSA).

Results

Hypothesis. A clinical states framework was used to address the hypothesis that definitive phase III trials could not be conducted in this patient population.

Patient Population. The Group focused on men with systemic (nonlocalized) recurrence and a defined risk of developing clinically detectable metastases. Models to define systemic versus local recurrence, and risk of metastatic progression were discussed.

Intervention. Therapies that have shown favorable effects in more advanced clinical states; meaningful biologic surrogates of activity linked with efficacy in other tumor types; and/or effects on a target or pathway known to contribute to prostate cancer progression in this state can be considered for evaluation.

Outcomes. An intervention-specific posttherapy PSA-based outcome definition that would justify further testing should be described at the outset.

Reporting. Trial reports should include a table showing the number of patients who achieve a specific PSA-based outcome, the number who remain enrolled onto the trial, and the number who came off study at different time points. The term PSA response should be abandoned.

Trial Design. The phases of drug development for this state are optimizing dose and schedule, demonstration of a treatment effect, and clinical benefit. To move a drug forward should require a high bar that includes no rise in PSA in a defined proportion of patients for a specified period of time at a minimum. Agents that do not produce this effect can only be tested in combination. The preferred end point of clinical benefit is prostate cancer-specific survival; the time to development of metastatic disease is an alternative.

Conclusion

Methodology to show that an intervention alters the natural history of prostate cancer is described. At each stage of development, only agents with sufficient activity should be moved forward.

J Clin Oncol 22:537-556. © 2004 by American Society of Clinical Oncology

INTRODUCTION

The disease-related mortality of prostate cancer has decreased during the last 3 years [1]. Nonetheless, about 28,900 men are projected to die in the year 2003, and the disease remains the second most common cause of

cancer death in males in the United States. A long-held paradigm in oncology is that early diagnosis and treatment will enhance cure rates and improve survival. International trends show that more men are being diagnosed with and treated for prostate cancer at an earlier point in the illness than in the past.

In part, this is due to the more widespread use of early detection strategies that include the measurement of prostate-specific antigen (PSA) levels in the blood. No tumor marker has had as great an impact on the diagnosis and management of a disease as has PSA level in prostate cancer, which has a role in screening, early detection, assessing outcomes, monitoring progression, and evaluating the effects of treatment.

The range of uses of the PSA test has sparked new questions and controversies. Whereas some investigators feel that the decline in the number of deaths from prostate cancer is a result of the introduction of PSA measurements in the late 1980s, others believe that the 10-year interval between the availability of the assay and the reduced number of deaths is too short to have had an appreciable impact on survival [2]. There is uncertainty about the significance of posttherapy changes in PSA as a treatment effect because levels may decline in the absence of an effect on tumor growth [3,4].

Perhaps the most controversial aspect of PSA monitoring is that it has created a new clinical state, one that includes men who have been treated with curative intent for localized disease in whom a rising PSA indicates treatment failure and is the sole manifestation of the illness. On the basis of the number of the men diagnosed with prostate cancer who undergo a radical prostatectomy or radiation therapy, and the estimated probabilities of relapse, upwards of 50,000 men per year in the United States fall into this clinical state [5]. Management is controversial, in large part because the natural history is so highly variable and the relationship between tumor mass and serum PSA value is less established [6].

The intent of any drug development effort is patient benefit, which includes to produce a favorable change in the natural history of the disease, to prolong life, or to alleviate or to prevent symptoms of disease. For some men, a rising PSA after primary therapy marks the beginning of progression to the lethal variants of the disease. For these individuals, early therapy may be life-saving. However, even though PSA elevations almost universally antedate progression on imaging studies and the onset of symptoms, a rising PSA level is not clinically significant for many men. For these individuals, the justification for treatment is less clear because they are asymptomatic from their cancer, and the risk of developing metastases, symptoms, or dying from the disease may be low during their anticipated life expectancy [7]. In the worst-case scenario, therapy may be detrimental and shorten survival.

The design, conduct, and interpretation of clinical trials in this patient population is not straightforward. For many researchers, it has become a minefield in which clinical trial resources are rapidly depleted to no concrete end. It is against this background that three meetings on Clinical Trials in the State of a Rising PSA were held on February 12

to 13, 2001 and June 18 to 19, 2001 in New York, NY, and June 24, 2002 in Washington, DC. A writing session was held in Chicago on February 25, 2003 and final discussion was conducted in Los Angeles, CA, on March 31, 2003. The Group focused on patients in whom the sole manifestation of disease was a rising PSA level and who had noncastrate levels of testosterone after definitive treatment of the primary tumor. Patients with a rising PSA after hormonal therapy were not included. The Group was organized by investigators from Memorial Sloan-Kettering Cancer Center (New York, NY), the Cancer Treatment Evaluation Program (CTEP) of the National Cancer Institute (Bethesda, MD), and the Association for the Cure of Cancer of the Prostate (Prostate Cancer Foundation, formerly CaP CURE; Santa Monica, CA). The participants were a multidisciplinary group of physicians and investigators representing the disciplines of urologic surgery, radiation oncology, medical oncology, clinical chemistry, and biostatistics from academic institutions, private foundations, patient advocates, oncology cooperative groups, governmental agencies (including the US Food and Drug Administration), and the pharmaceutical industry.

The objectives of the meeting were to address the following issues:

- Should this population of patients be targeted for drug development?
- How to define the clinical significance of a rising PSA after local therapy?
- How should outcomes be assessed?
- Can trial designs for the state of a rising PSA level be standardized?
- How can we prove that a treatment or intervention has altered, favorably or negatively, the untreated history of the disease?

The evaluation of a therapy or a treatment approach can be divided into five components: the hypothesis, the patient population in whom to test the hypothesis, the intervention, the outcome measure(s) and reporting, and the conclusions. The conclusions include the generation of additional hypotheses and a decision about whether the approach should be tested further. The Group discussed each aspect individually, with the aim of developing a framework for drug development for this patient population. The recommendations are summarized in Appendix A.

HYPOTHESIS

The initial hypothesis we explored was that phase III trials should not be conducted in this patient population because the prognosis of a man with a rising PSA level is not well defined; PSA levels are modulated by many factors and as such, posttherapy changes in PSA may not reflect changes in

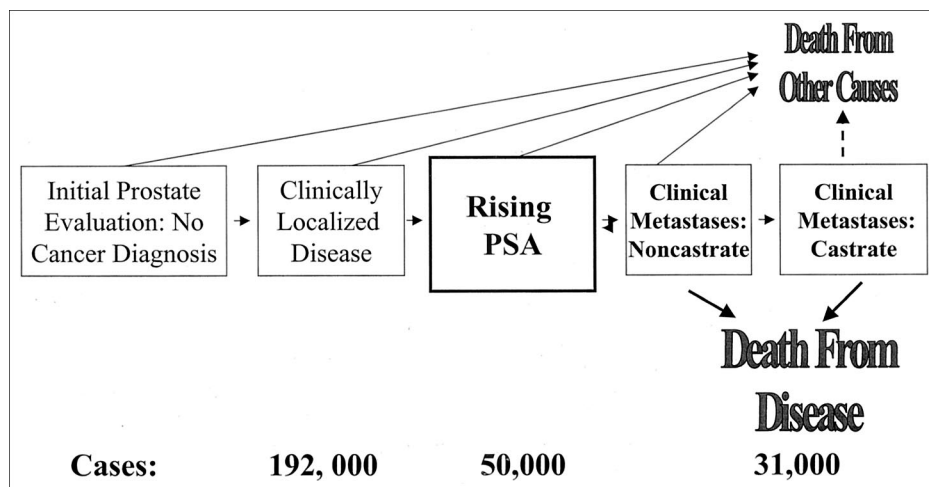


Fig 1. A clinical states model of prostate cancer development and progression to define therapeutic objectives and to assess outcomes: The model highlights the competing risks of mortality from prostate cancer versus death from other causes, and how slowing progression may be tantamount to cure without eliminating the last cancer cell. Adapted from [1] with permission.

tumor cell growth or proliferation; there is no uniform or meaningful definition of a PSA response or outcome that has been shown to reflect a change in the natural history of the disease; and many patients will not continue to receive therapy until an end point of radiographic progression or death from disease has been reached if their PSA levels continue to rise. Most receive androgen-ablative therapies, which lower PSA levels and delay metastatic progression, hampering the interpretation of the effect of the primary treatment administered.

To frame the discussion, the Group adopted a clinical states model that describes the management and progression history of prostate cancer (Fig 1) [8]. Unlike the standard tumor-node-metastasis system staging system, which applies to patients only at the point of diagnosis, the clinical states model describes untreated and treated patients from before diagnosis to death. A patient resides in only one state at any point in time. At each clinical encounter the patient is assessed using demographic, clinical, biochemical, or other biologic determinants to predict a probability of progressing to the next clinical state, of developing symptoms, or dying as a result of the disease. The framework has been validated further in Markov models of the disease [9,10].

By addressing the reasons why trials should not be conducted in this patient population, the Group developed a trial methodology that would ultimately provide evidence of clinical benefit. The first issue was to determine whether the rise is the result of persistent local disease, a systemic failure, or both. For those with systemic disease, drug development efforts should focus on cohorts of patients who have a high probability of developing a clinically meaningful event (eg, bone metastases or detectable metastatic disease on an imaging modality, or prostate cancer–specific death) in a predetermined period of time. This restricts therapy to those who require it and allows treatment effects to be assessed in a reasonable time frame. The probability of

developing the event and the time frame for its development are debatable [8]. Accurate estimates of the number of important clinical events within a specified observation period are crucial for trial design [7].

PATIENT POPULATION

The following aspects of the patient population were considered: when has a patient entered the state of a rising PSA; whether the PSA rise represents persistent or recurrent local disease, systemic disease, or both; and determining the probability that a patient with a systemic relapse will develop clinically detectable disease and in what time frame. Recognizing the uncertainties for each of these assessments, the Group proposed eligibility criteria for enrollment of men in clinical trials (Table 1).

Defining When a Patient Occupies the Clinical State of Rising PSA

A patient is considered to have entered the clinical state of rising PSA when the PSA value begins to rise after surgery or radiation therapy excluding hormonal therapy alone. It was agreed that patients with rising PSA levels who have not undergone definitive local therapy should not be included. Such patients have existing localized disease and their rise in PSA does not necessarily represent a state transition to micrometastatic disease. The PSA-based definition of progression (biochemical failure after primary therapy) varies by the specific local therapy that the patient had received and by the sensitivity of the assay used to measure the enzyme. PSA levels also vary with the level of testosterone, which is affected by the duration of androgen deprivation for patients treated with a combined-modality approach. Testosterone levels should be measured for all patients enrolled onto a trial. In general, testosterone levels return to baseline within 3 to 6 months after cessation of short-term

Table 1. Eligibility for Trials in Patients With a Rising PSA

Record
PSA, T stage, and Gleason score at the time of diagnosis
Primary therapy and outcome (if surgery, pathologic stage and nodal status)
Neoadjuvant or adjuvant therapies, if any
Time to failure
Rising PSA: patients with a history of localized disease who have undergone definitive treatment of the primary tumor
Post-radical prostatectomy
Minimum number of determinations, 3
PSA level > 0.4 ng/dL, and rising that is documented on three occasions 2 or more weeks apart.
Post-radiation therapy
Minimum number of PSA determinations, 3
Interval between PSA determinations > 2 weeks
Minimum value above 1.5 ng/dL at the time of enrollment
Exclude local failure: biopsy if clinically indicated
No evidence of metastatic disease on physical examination or on CT (MRI) and bone scan
CT scan (or MRI) and bone scan
TRUS, MRI, PET, and Prostatecint are experimental
Hormonal status: patients may have received prior hormone therapy as part of definitive treatment. (Duration should be recorded.)
Not receiving therapy(ies) that modulate testosterone levels (eg, hormonal therapy, such as antiandrogen therapy) or alternative treatments, for a minimum of 1 year.
Testosterone: Testosterone level > 150 ng/dL
PSA doubling time: to obtain results in a reasonable time frame, it is suggested that trials be restricted to patients with PSA doubling times of less than 12 months
There was no consensus on the maximum PSA level
Abbreviations: PSA, prostate-specific antigen; CT, computed tomography; MRI, magnetic resonance imaging; TRUS, transrectal ultrasonography; PET, positron emission tomography.

gonadotropin-releasing hormone analog treatment, but the recovery is highly variable in individual patients [11,12]. Older age and prolonged androgen deprivation are associated with a longer time to recovery of physiologic levels. Wide variations based on the type of preparation (eg, 1 v 3 month depot) have been observed [13]. Estrogen- or estramustine-based treatments produce more prolonged testosterone suppression. Some clinicians recommend recording PSA and testosterone levels concomitantly, and define failure as when a patient has had the requisite number of PSA increases and the testosterone level has reached a plateau (two consecutive testosterone measurements within 10% of each other) [14]. Others suggest requiring that the measured testosterone be more than 150 ng/dL before enrolling a patient onto a clinical trial. This cutoff requires prospective validation. For those who have received hormone therapy, it was suggested that the testosterone level reach a plateau or return to the pretreatment baseline, and that it be monitored serially throughout the trial.

Radical prostatectomy. A patient is considered to have progressed following a radical prostatectomy if PSA is detectable 8 weeks or more after the procedure, and a subsequent value is rising. This exceeds the time that PSA should be cleared from the blood on the basis of a half-life of 2 to 3 days [15]. The treatment failure is considered to occur the date the PSA becomes detectable. There is debate about whether the level of PSA signifying failure should be ≥ 0.2 or ≥ 0.4 ng/mL, [16], recognizing that levels as low as 0.01

to 0.07 ng/dL might represent recurrent disease if an ultrasensitive assay were used, and that benign glands at the margin can produce low levels of PSA, and may not necessarily represent recurrent cancer. Whether a value below 0.2 is predictive of true recurrence was not considered further [16-18]. Also discussed was whether a patient in whom the PSA did not reach an undetectable level should be included in this disease state. The consensus was that they should, assuming that the resection was found to be complete, there was no lymph node involvement, and the margins were negative.

The minimum PSA level to consider a patient eligible for clinical trials in this state was arbitrarily defined as a value ≥ 0.4 ng/mL at a minimum of 1 month after surgery, which is confirmed on a subsequent test followed by a value equal to or greater than the previous value. This decision was based on the supposition that patients with a PSA level of 0.4 or greater are at a higher risk of systemic relapse [19].

Radiation therapy. Radiation therapy is administered by external-beam techniques alone, implants alone, or a combination of the two. Often, hormones are used before, concurrently, and/or after radiation at intervals ranging from months to years. The American Society for Therapeutic Radiation Oncology (ASTRO) has developed a consensus definition for biochemical failure after radiotherapy as three consecutive rises in PSA starting at least 2 years after the start of radiation, with the time of failure as the midpoint between the nadir and the first confirmed rise [20]. It

is recommended but not required that there be a minimum of 3 months between measurements. However, transient rises in PSA can confound the determination of relapse. Shortcomings of the ASTRO definition are the requirement that the PSA rises be consecutive, and the lack of a defined magnitude of PSA rise that signifies failure. Proposed modifications to the Consensus definition are to relax the requirement that the three rises be consecutive [21].

The absolute value of PSA that qualifies as disease recurrence after radiation therapy is controversial. Values of 1.0, 1.5, 2.0, and 2.5 ng/mL have been considered on the basis of a receiver operating curve analyses. Others recommend values of 0.5 or 1.0 ng/mL as more predictive [22]. More important than the absolute value of PSA is to use caution when interpreting isolated increases in the marker. These so called bounces in PSA have been reported in 12% to 61% of cases 18 to 36 months after treatment [23]. Bounces occur more commonly in patients treated with brachytherapy, showing the importance of confirming a rise in value with serial measurements over time. It was suggested that the distinction between bounce and failure can be made more precisely if values are collected over an interval of 9 months to a year [24,25]. Unfortunately, rules to differentiate between these benign bounces and true recurrent disease have not been validated [26]. For enrollment in clinical trials, a minimum value of 1.5 ng/mL was suggested.

Calculation of Doubling Time

PSA doubling time (PSA-DT) defines the rate of change in serum PSA over time. Although this determination would seem to be straightforward, there are uncertainties in the calculation. The uncertainties include whether PSA-DT should be based on threshold values, whether PSA rises should be consecutive, the minimum number of samples on which to base the calculation, the frequency at which the samples should be obtained, and the interval over which the measurements are determined. Most calculations are based on a first-order kinetics assumption where $PSA(t) = PSA(0)e^{at}$ and a is the relative velocity of PSA. Some investigators mandate a minimum of three PSA values, each separated in time by at least 3 months, with a minimum difference of 0.2 ng/mL between each value. Unfortunately, one third of the PSA profiles in this patient population follow higher-order kinetics [27,28]. Thus, the equation used for doubling time may be suboptimal for approximately one third of the PSA profiles. Higher-order mathematical methods may better describe the PSA profiles for these men.

The rate of testosterone recovery after neoadjuvant therapy can affect the calculation of PSA-DTs. A slow recovery may result in doubling time calculations that are artificially long and in the inappropriate assignment in a low-risk category. A rapid recovery may result in the

inappropriate classification of a patient as high risk. Herbal supplements such as PC-SPES may lower testosterone levels and lower PSA [29], whereas inflammatory processes may falsely increase levels. To circumvent this, some clinicians begin the estimation of doubling times when the testosterone level is a minimum of 150 ng/mL on two determinations.

Determining Whether the Relapse Is Local or Systemic

Determining whether a rising PSA level is due to local disease exclusively is important because of the potential that additional therapy to the primary site may be curative. Unfortunately, the methods to exclude distant metastases are insensitive. Furthermore, even if local disease is detected, it does not rule out the presence of micrometastases, which is consistent with the low cure rates associated with salvage local therapy [30,31].

Imaging. The traditional imaging evaluation to detect metastatic disease is a bone scan, computed tomography (CT) scan of the abdomen and pelvis, or magnetic resonance imaging (MRI). Transrectal ultrasound (TRUS), positron emission tomography (PET), and ProstaScint scans are all under active investigation to detect local and systemic disease.

CT is relatively insensitive, with a lower limit of detection of 0.5 cm. CT scans are also nonspecific; abnormalities may signify fibrosis or a scar rather than tumor [32].

Bone scans measure the osteoblastic response to tumor in the marrow, and not the marrow metastases themselves. Lesions must be a minimum of 0.4 cm to be detected. In one study, the frequency of a positive bone scan in patients with a PSA recurrence after radical prostatectomy was low until levels were in the range of 30 to 40 ng/mL [33].

MRI, with an endorectal coil and specific acquisition algorithm that focuses on the pelvis, may reveal atypical sites of recurrence around the bladder and prostate bed. Some of these sites are in areas that are not routinely sampled using standard biopsy algorithms [34]. The value of MRI is not proven in this clinical setting at this time.

TRUS is also under study as a modality to detect residual disease in the prostate for the patient who has been treated with radiation therapy [35,36].

PET can detect areas of abnormal metabolism. It offers the potential to image sites in bone and soft tissue simultaneously, and to survey the entire body rapidly. The lower limit of detection with respect to lesion size, metabolic activity, and PSA level is uncertain. One study showed that the frequency of abnormal sites of metabolism increased with the absolute level of PSA and the PSA-DT. Abnormal areas of uptake were identified in the mediastinum and lung, sites that are not routinely evaluated using transaxial imaging [37].

ProstaScint scans are the only test approved by the US

Food and Drug Administration to detect disease in patients with early prostate cancer, but its role in managing a patient in the state of a rising PSA is uncertain. This immunoconjugate consists of a murine antibody to prostate-specific membrane antigen that is labeled with 111-indium. Unfortunately, the test is associated with a significant number of false-positive and false-negative results, in part related to nonspecific localization of the antibody to the gastrointestinal tract [38], inflammation, and vascular sludge [39]. Use at this time is controversial. At issue is whether a ProstaScint scan that predicts for disease beyond the prostate bed has been or can be confirmed by the demonstration of disease on a conventional imaging modality, surgery, or by biopsy [40]. A re-evaluation of the utility of ProstaScint scans with fusion imaging is ongoing.

Biopsy of the prostatic fossa after radical prostatectomy. After surgery, it is advised that palpable and visible abnormalities in the prostate bed be biopsied to confirm recurrence. It is also believed by many clinicians that a biopsy is not indicated in the absence of palpable abnormalities because of the possibility of sampling error, and because the decision to administer and the response to salvage radiation therapy are often not affected by the results [30].

Biopsy of the prostate after radiation therapy. The decision to perform a biopsy after radiation therapy will depend on whether the patient is a candidate for a salvage radical prostatectomy or other prostate-directed therapy such as cryosurgery [41], brachytherapy [42], or intraprostatic biologic or cytotoxic treatment. If so, documenting persistent and viable disease in the prostate is essential. A minimum of 2 years should have elapsed from the completion of radiation therapy to diminish the risk of false-positive results.

Prognostic models. Although the definitions of risk vary, patients who are at high risk for recurrence at the time of diagnosis have the highest risk of developing clinical metastatic disease and dying from prostate cancer when they experience treatment failure. The models used to estimate the likelihood of PSA relapse-free survival, risk of local versus systemic relapse, risk of developing metastatic disease after PSA failure, or risk of death as a result of disease fall into four categories: models predicting PSA failure [43-45]; models predicting the probability of a given pathologic stage [46-48]; models predicting probability of death [49-52]; and empirically developed mathematical models (nomograms) for these same outcomes [21]. These models are being updated and refined on a regular basis. In general, the most informative models include determinants that reflect the tumor at the time of initial diagnosis and treatment, the time to PSA failure, and PSA-DT. All of the models work in defining what they are designed to predict. In many analyses, baseline value PSA is the most important predictor of PSA failure, but may not be the most important predictor of prostate cancer-specific death.

Predicting local versus systemic relapse. Lower baseline PSA levels, lower Gleason scores, lower T stages, longer time to PSA relapse, and slow doubling times are associated with local as opposed to a systemic relapse [8]. In one study, local recurrence was predicted by the pretherapy PSA value, PSA-DT, and findings on digital rectal examination, whereas durable response to radiation therapy was predicted by the baseline PSA value and PSA-DT [6,30]. Others have used outcomes from salvage radiation therapy after radical prostatectomy as a way to predict that a rise in PSA after radical prostatectomy was due to local disease alone. In one such trial, pathologic predictors for a response to salvage radiation were negative or close margins ($P = .03$), absence of extracapsular extension ($P < .01$), and presence of seminal vesicle invasion ($P < .01$) [53]. A nomogram based on long-term PSA control after radiation therapy to the primary that incorporates pathologic features of the radical prostatectomy specimen, time to PSA relapse, absolute value of PSA, and PSA-DTs was recently reported [54].

Risk of a state transition to clinical metastatic disease. Pound et al [8] evaluated a cohort of men who developed an isolated PSA recurrence after radical prostatectomy and who were not treated further until symptomatic or radiographic evidence of disease progression. The factors that independently predicted for progression were surgical Gleason score, interval to first detectable PSA (≤ 2 v > 2 years), and PSA-DT (< 10 v ≥ 10 months). In an updated analysis, time to PSA failure was no longer predictive when PSA-DT was considered [55]. In a separate analysis, 5-year systemic progression-free survivals exceeded 93% in patients with doubling times greater than 6 months versus 64% for those with doubling times less than 6 months [56]. With longer follow-up, PSA-DT has replaced both prostatectomy Gleason score and time to PSA failure in predicting time to bone metastases after PSA failure [55]. Other groups have reported similar differences in time to detection of clinical metastatic disease based on rapid versus slow doubling time estimates with different cut points [52,57].

Risk of death as a result of prostate cancer. Models that define the risk of prostate cancer-specific death for patients with a rising marker are just beginning to be developed as the data from trials of patients with high risk localized disease mature. An example is the reported link between PSA-DT and time to PSA recurrence, with distant progression or cause-specific survival after primary radiation therapy [58-62]. These associations are important when trying to determine who needs treatment to prevent clinically significant disease-related events. It is also important when designing trials using non-PSA-based end points. In more recent analyses, a PSA-DT of less than 3 months and the specific value of PSA-DT when 3 months or more have elapsed after either radical prostatectomy or external-beam radiation therapy, were shown to be a surrogate for time to prostate cancer-specific mortality after PSA failure [63]. On

the basis of these data, PSA-DT should be considered a stratification factor when selecting patients with noncastrate disease and a rising PSA for clinical trials.

THE INTERVENTION

Studies of the mechanisms and factors associated with the development, growth, and spread of prostate cancer have resulted in new targets for therapy and new drug classes that fall beyond the traditional hormones and cytotoxic agents. Included are drugs designed to alter tumor growth rates, differentiate cells, affect points in the metastatic cascade, or elicit a host immune response. More important is that for many of these agents, the classical phase I paradigms that seek to define a maximum-tolerated dose may not apply. In theory, any class of drug can be evaluated in this population. The question is at what point in the development of a compound or treatment approach should patients with a rising PSA be studied?

It was the consensus of the group that human testing of a new substance should rarely begin in this population until the safety profile is understood and preliminary evidence of an antiprostate cancer effect are available. Most compounds that are destined to show activity in this clinical state will also be active in patients representing more advanced clinical states in which treatment effects can be assessed more clearly. As such, most compounds will tend to be evaluated first in patients who have experienced disease progression while receiving hormones, and will not be tested in the state of the rising PSA unless some measures of benefit are shown in more advanced disease. This is particularly the case for cytotoxic agents, for which the risks of acute and chronic effects are not generally considered justified in an asymptomatic population with a long life expectancy.

There are notable exceptions. For example, immunologic approaches may only be effective when tumor burden is minimal (ie, in the state of a rising PSA) or after cytoreduction with surgery, hormones, or chemotherapy. Therapies directed at targets that are unique to the state of a rising PSA (noncastrate disease), for example, a target modulated by androgens, may not be effective in states in which the target is not present. Factors to be considered when trying to determine whether to study compounds in this state include the therapeutic class, the anticipated biologic effect, the putative mechanism, the anticipated effect on PSA independent of cell kill, whether the drug is best administered on an acute or chronic basis, and the anticipated side effects. It was suggested that the drug be tested *in vitro* or *in vivo* using PSA-secreting cells and/or xenografts, to determine what the effects of the drug are on PSA expression, with the caveat that these assays are themselves investigational. This information can be useful in the selection of outcome measures that will be used to assess treatment effects, both positive and negative. Such testing is not possible for agents

that are only activated *in vivo* or that function by eliciting a host response.

MEASURING OUTCOMES AND REPORTING

Much of the debate in prostate cancer has been about the standardization of outcomes and not enough on the clinical significance of the outcomes.

Measuring Outcomes

Outcome measures are required to decide if a patient is or is not benefiting from a treatment, and more globally, whether a treatment is effective. Standardization of outcomes in the form of response criteria has helped bring order to the chaos of reporting the results of clinical trials. Much has been accomplished in trials of patients with progressive castrate metastatic disease [64] and, in more general terms, the Response Evaluation Criteria in Solid Tumors Group criteria were recently reported and adapted by the Cancer Therapy Evaluation Program for clinical trials in solid tumor malignancies [65]. Difficulties in applying the PSA Working Group criteria to trials for patients in the state of a rising PSA are that there are no radiographic findings, symptoms, or pathologic specimens that can be used in addition to PSA changes as outcome measures, and the PSA-based criteria are not applicable in all contexts. Response Evaluation Criteria in Solid Tumors Group criteria do not consider markers. For patients in this clinical state, there are several useful end points: a defined change in the level of PSA or PSA kinetics, a delay in a clinically significant event such as the development of disease that can be detected by imaging or physical examination, symptoms or death as a result of disease, and the risk-to-reward ratio of the intervention versus no intervention. Both present problems because there is no universal set of PSA-based rules that will be applicable to agents with diverse mechanisms of action; in addition, many patients will not remain under observation until the clinically significant event occurs if the PSA continues to rise. This makes the risk-to-reward ratio difficult to quantitate.

Posttherapy Changes in PSA

The attraction of measuring serial PSA levels is that these assays can be obtained simply and frequently with minimal inconvenience to the patient. However, ease of measurement and seeming mathematical objectivity should not be confused with patient utility or surrogacy. A surrogate end point is an outcome variable that can substitute for a definitive end point and does not alter the inference on the treatment effect. Surrogates occur with sufficient frequency in a reasonable time frame, and can be measured more easily and reproducibly with smaller sample sizes. Posttherapy changes in PSA have not been associated with delaying the development of metastases or prolongation of life in a prospective randomized trial. As such, posttherapy changes in PSA have not met

the criteria for surrogacy, and it was the consensus of the Group that they not be used as the sole indicator of clinical benefit. A weak association between postbiopsy decrease in PSA value and survival in castration-resistant disease has been shown [66], but not in hormone-naïve disease.

The central issue is whether or not posttherapy PSA change criteria can be defined for an individual patient or for a population of patients treated with a specific therapy that can be used to determine whether treatment or clinical development should continue. The posttherapy measure could be a decline, a stabilization, or a decrease in the rate of rise. For those therapies that produce the defined effect, development continues, and for those that do not, further development ceases. The timing of the effect is also a consideration. Knowledge of the drug or combination of agents under study is essential to define or to anticipate the interval to PSA decline. Different posttherapy PSA change definitions will be required for agents that act via different mechanisms.

Hypothetical posttherapy PSA patterns are illustrated in Figure 2. In each case, a pretherapy PSA rise is documented to estimate the rate of rise or doubling time, with the start of treatment indicated by the arrow (\uparrow). Figure 2A shows a treatment that has produced an undetectable PSA that is prolonged, as might be seen with androgen ablation or an effective cytotoxic agent. Figure 2B illustrates the same rapid decline that is followed by an escape. Figure 2C shows no change or a plateau in PSA that might occur for an approach that produces a cytostatic as opposed to cytotoxic effect. Figure 2D shows what might occur with a biologic agent that does not elicit an effect for a period of time. In such a case, the PSA level will continue to rise until the effect is fully manifest. In contrast, Figure 2E shows what might occur if a differentiating agent such as a retinoid were used in which there is a paradoxical increase in PSA in the short term followed by a decline. The important consideration is that the initial increase in PSA level does not necessarily indicate treatment failure [67,68]. Figure 2F illustrates what has been termed a broken arrow, in which the rate of rise was slowed but continues to rise; Figure 2G shows a similar outcome after a delay. The important factor is that the timing of the posttherapy measurements must account for these variations so that patients are not withdrawn from a trial prematurely. Finally, Figure 2H shows a treatment that has not altered the rate of rise in PSA. Although this pattern may represent a drug with no effect on the disease, it may also represent a drug that reduces that rate of metastases or delays the development of metastases without killing cells. Such an effect may be observed with bisphosphonates, which have been shown to delay metastatic progression in bone without affecting PSA [69]. In this case, a beneficial therapy could easily be missed.

PSA-Based Definitions of Progression

The definition of progression on the basis of PSA is highly variable. In some cases it is defined by an increase to a predetermined number, in some cases it is defined by an increase by an absolute percentage, and in other cases it is defined by a change in the postintervention rate of rise. The definition must also vary for drugs that produce no change, those that produce a decline, or those that produced an undetectable PSA. Examples of different definitions of failure or relapse on the estimation of time to progression calculated from the start of therapy are shown in Figure 3A and 3B. In Figure 3A, the intervention produced a posttherapy PSA decline of 80% (point a) that was documented several times. This was followed by a period of no change (stability), after which elevations were observed (points b, c, and d). At point b (line 1), the time of PSA progression was recorded as the first confirmed rise in PSA. Alternatively, a variant of the ASTRO definition could be used, which is the midpoint of nadir and the first confirmed rise [20]. At point c (line 2), PSA progression is marked at the point the level has returned to 50% of the baseline value, as proposed for trials in patients with androgen-independent (castration resistant) disease [64]. Alternatively, a 50% increase from the nadir can be used. This too is problematic, as shown by point d (the point of the first confirmed rise in the lower line), for levels that continue to increase but never reach the point of a 50% increase from baseline or nadir. As illustrated, the compound could be considered to have a short, intermediate, or more durable effect. It is for this reason that the time to the first confirmed rise is preferred [68]. Finally, in situations in which treatments produce an undetectable PSA, the time to a detectable PSA value would be considered progression. Figure 3B shows the difficulties that can arise when trying to define a date or time to progression for drugs that slow the rate of rise without an initial decline or stability, or for drugs for which the effect, if it is to occur, is delayed. Line 1 shows the slope of the change based on the pretherapy rate of rise, and line 2 shows the slope of the posttherapy rate of rise. Which definition is used should be stated clearly in the trial.

Regardless of the definition used, simply determining that a proportion of patients satisfy the outcome definition is only one part of the equation. Ultimately, the decision to move forward must also factor in the duration of the effect. A short dramatic decrease in PSA may not be as important as a sustained decrease, even if it is not of the same magnitude. Similarly, a decline in the slope of the PSA curve for 2 weeks may not be significant, but a decline in the slope of the PSA curve for 2 years might be worthy of continued study. These caveats notwithstanding, posttherapy changes in PSA can still be of use to screen for activity and to determine whether the development of a compound should stop or should continue.

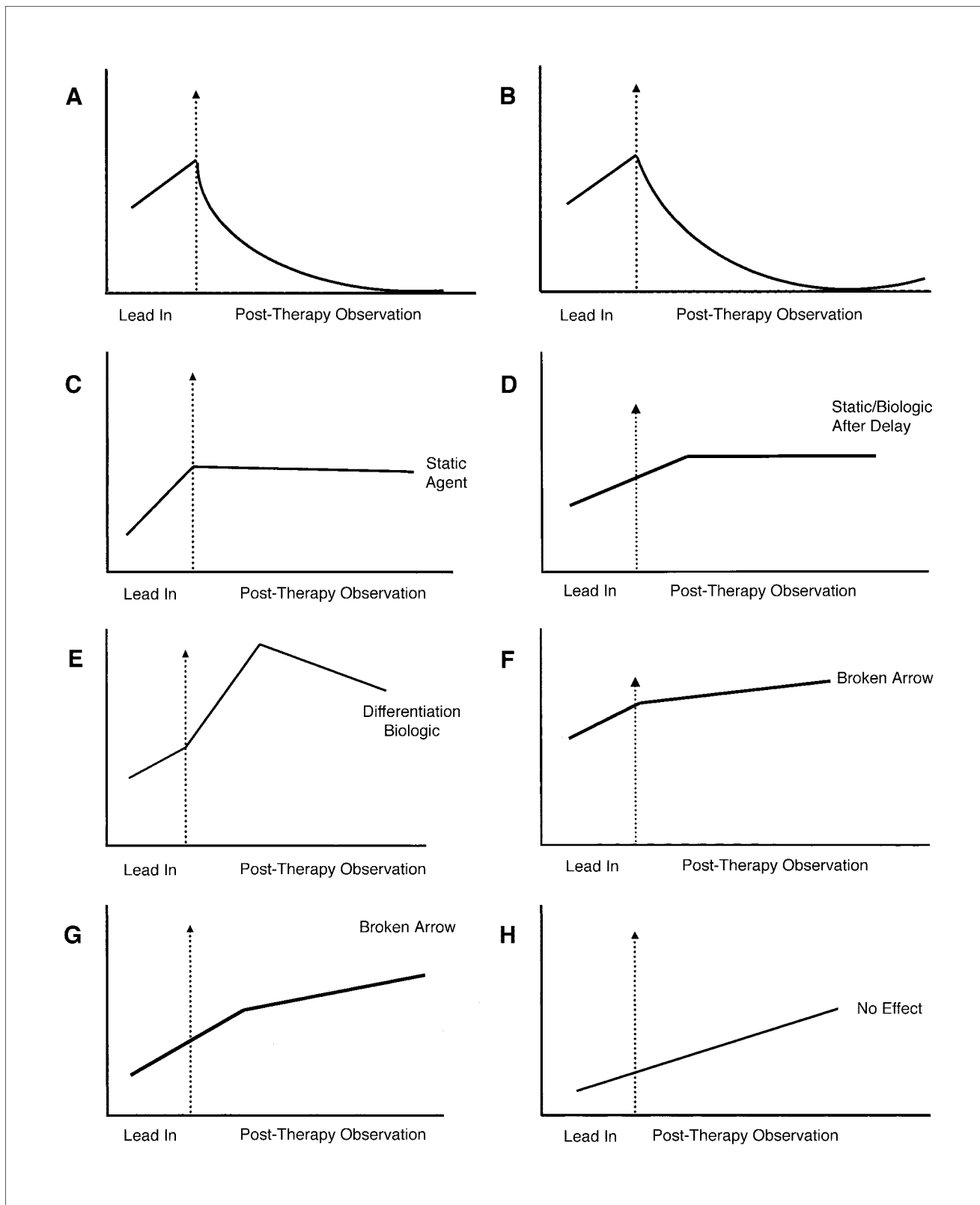


Fig 2. Posttherapy PSA patterns following different interventions in a patient with a rising PSA: The start of treatment is indicated by the arrow (\uparrow). (A) rapid decline with no escape; (B) rapid decline followed by escape; (C) a “no change” or plateau (2 days); (D) similar to (C) but only after a delay; (E) an initial rise followed by decline; (F) a “broken arrow” in which the rate of rise was slowed; (G) similar to (F) with a delayed effect (2 hours); a treatment with no effect on PSA. (For details see text).

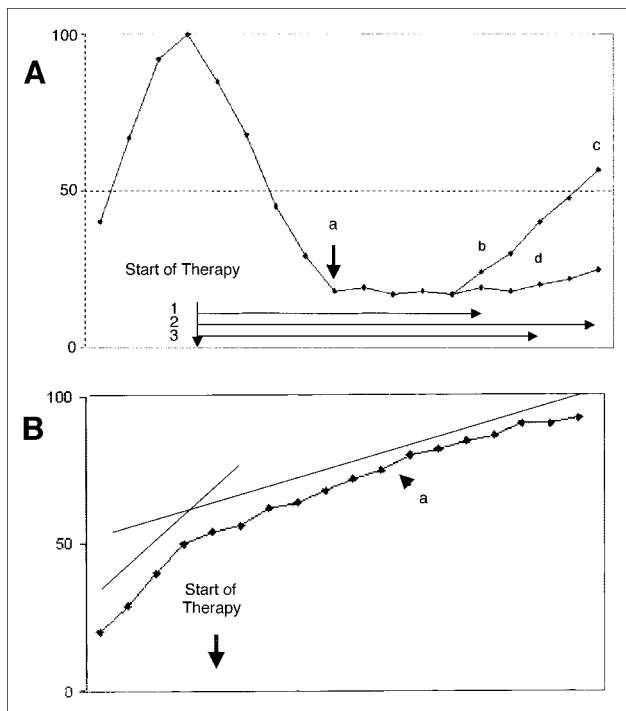


Fig 3. Effect of different definitions of failure or relapse on the estimation of time to progression calculated from the start of therapy: (3A) Line 1—failure defined as the first confirmed rise (point b); Line 2—failure defined by the PSA Working Group for castration resistant disease, [64]; Line 3—failure defined as first confirmed rise when increase did not exceed 25% from the treatment nadir. (3B) Illustrates PSA levels in a patient for whom treatment slowed the rate of rise in PSA. Line 1 is the pretherapy slope and line 2 the posttherapy slope (For details see text).

Reporting

For consistency, the Group recommended that outcomes be reported in a tabular format that records the number of patients who meet different PSA-based outcomes at defined posttreatment intervals (Table 2). The table includes the number of patients enrolled, the number of patients at fixed time points after therapy, and the number meeting specific PSA-based criteria. The number who continue to receive treatment and who have discontinued treatment are also recorded. The reason a patient was taken off study should also be recorded, be it the development of clinically detectable metastatic and/or local disease, adverse event, anxiety, or the administration of a different treatment for any reason. This approach allows a rapid visualization of the proportion of patients who have met a specific outcome criterion and who have not undergone a transition to a more advanced state.

TRIAL DESIGN

The clinical evaluation of any therapy involves a series of trials, each of which determines whether or not to continue development. The trials are classified traditionally into one of three phases: phase I trials define a dose and schedule,

phase II trials seek evidence of a biologic effect in a disease or disease state of interest, and phase III trials are designed to establish efficacy and safety of the new approach in comparison with an established standard of care or placebo. There are difficulties applying this paradigm to trials in the state of a rising PSA because, in most cases it is not appropriate to explore the traditional end point of maximum-tolerated dose (MTD) of an unknown compound in an asymptomatic population with a long life expectancy; typical phase I trials focus on acute as opposed to chronic dosing schedules; it is difficult to compare outcomes on the basis of different posttherapy PSA-based end points; and patients enrolled onto trials designed to show clinical benefit will not remain on a trial when their PSA levels are rising until an objective end point (such as the appearance of disease on an imaging study or physical examination) is reached.

As noted previously, there was consensus that the clinical evaluation of a drug should rarely begin in patients with a rising PSA. Such is the case whether the drug is a cytotoxic, a mechanism-based therapy that has already been given to normal volunteers, or a potentially new use for a drug approved for noncancer indications and for which the safety of long-term administration has already been demonstrated. The challenge is to design informative trials that demonstrate objectively whether an approach is beneficial to this patient population, and to what degree, so that they can be prioritized for further development. To do so requires a new paradigm that addresses issues in three general categories: dose and schedule, treatment or biologic effect, and clinical benefit (Table 3)

Dose and Schedule

The first consideration for dose and schedule is whether the treatment is being developed to cure the disease by eliminating the last cancer cell, or to control the disease by preventing a transition to a state of clinical metastases. For slower-growing cancers, control may be tantamount to cure, despite the fact that PSA levels are detectable and rising throughout a patient's lifetime.

Dosing for cure. In theory, a systemic therapy with activity in late-stage disease may be more efficacious in a minimal disease setting (low tumor burden), such as rising PSA state. In gastrointestinal [70], thoracic, and breast malignancies [71], agents with modest activity in advanced disease have been shown in prospective randomized comparisons to increase cure rates when used in the adjuvant setting. Even though the response proportions with chemotherapy in prostate cancer are equivalent to or exceed those of the diseases just cited, clinical testing in early-stage tumors has been limited. As the trials are planned, it is likely that many will involve agents with steep dose-rate/dose-response relationships for which toxicity issues, both short term and long term, will be dose limiting. For agents for

Table 2. Reporting As a Time to Event

Regimen 1: Tabular Summary of the Outcome of Patients With a Low Rate of Durable Declines in PSA and High Rate of Metastatic Progression							
Outcome	Entry	Follow-Up (months)					
		6	12	18	24	30	36
No. of patients	100	90	65	50	40	30	15
% change in PSA from baseline							
Greater than 50% increase		0	5	5	5	10	5
Increase of 10–50%		10	15	5	5	10	5
Between 10% decrease and 10% increase		30	20	20	15	5	5
Decrease of 10–50%		40	20	10	15	5	0
Greater than 50% decrease		10	5	0	0	0	0
Removed from study							
Objective progression		0	5	5	0	5	8
Death as a result of other causes		0	0	0	0	0	2
Rising PSA		5	15	5	10	3	5
Toxicity		5	5	5	0	2	0
Regimen 2: Tabular Summary of a Regimen Showing Durable Declines in PSA and a Low Rate of Objective Metastatic Progression							
Outcome	Entry	Follow-Up (months)					
		6	12	18	24	30	36
No. of patients	100	90	80	70	55	50	40
% change in PSA from baseline							
Greater than 50% increase		0	0	5	0	0	0
Increase of 10–50%		10	10	5	5	5	10
Between 10% decrease and 10% increase		30	30	30	25	20	15
Decrease of 10–50%		30	30	20	15	15	10
Greater than 50% decrease		20	10	10	10	10	5
Removed from study							
Objective progression		0	0	5	0	0	0
Death as a result of other causes		0	0	0	0	0	0
Rising PSA	10	6	5	10	5	10	
Toxicity		0	4	0	0	0	0

Abbreviation: PSA, prostate-specific antigen.

which toxicities are not anticipated to be dose limiting, the issue is to establish a dose that produces a biologic effect, and to show that the biologic effect is clinically relevant. This will be discussed in more detail below.

Dosing for cancer control. The traditional management approach considers prostate cancer a chronic disease. The

issue is to determine a dose and schedule that achieves and maintains a biologically relevant effect for a prolonged period of time with good patient tolerance (an acceptable safety profile). Before evaluations of efficacy (treatment effect) can proceed, knowledge that a biologically relevant dose has been administered is critical—failure is guaranteed if an effective dose is not given. This is not straightforward, because measuring changes in the growth of prostate cancer cells in patients with a rising PSA as the sole manifestation of disease exceeds the technologies currently available, and a favorable effect on PSA may not be a surrogate for an antitumor effect [4,5,72]. As a result, we are often forced to base our dosing schema on other intermediate measures.

The intermediate measures can be classified into three categories (Table 4): direct measures of inhibition of the growth of prostate cancers representing more advanced clinical states; anticancer effects in other diseases in which the surrogate for a biologic effect is known but which are not specific to prostate cancer; and effects on normal tissues (Table 5). Regression of soft tissue masses and improve-

Table 3. Design Objectives for Trials in the State of a Rising PSA

Dose and schedule
Dosing for cure
Cancer control: prostate cancer as a chronic disease
Treatment effect
Define an intervention specific post-therapy PSA change that would be considered favorable
Determining the proportion of treated patients who show the change
Determining the significance and durability of the effect by measuring the proportion of patients who do not develop metastatic disease at different time points after treatment
Clinical benefit
No objective progression on physical examination or imaging study
Abbreviation: PSA, prostate-specific antigen.

Table 4. Intermediate Measures to Optimize Dose

Direct measures on prostate cancers in more advanced clinical states
Effects observed in other diseases in which the surrogate for a biologic effect is known but which are not specific to prostate cancer
Normal tissues: peripheral blood mononuclear cells, buccal mucosa, skin, or hair follicles

ment in bone scan are the most direct. An advantage of studying other tumor types and normal tissues is that they are often more amenable to serial sampling, which allows the dose-time relationships to be worked out more precisely. Preclinical studies in prostate cancer xenograft models can also be used to optimize the timing of tissue sampling by monitoring changes in protein targets [73], or by functional imaging such as positron emission tomography [74].

Measures and outcomes from trials in prostate cancers representing more advanced clinical states provide the best rationale for testing in patients with a rising PSA. Outcomes that would lead to trials in early disease include shrinkage, or for a noncytotoxic drug, prolonged time to progression. An issue for targeted therapies directed at a specific signaling pathway is to ensure that the target or pathway is contributing to the growth of the disease in the state of a rising PSA level, and is not restricted to pathways associated with or specific to more advanced disease. It cannot be assumed that drugs targeting pathways present in castration-resistant disease are present and functional in the state of a rising PSA [75,76].

Effects observed in different diseases in which the surrogate for a biologic effect is known can also be used to develop dosing schedules for testing drugs in the rising PSA state. A marker or intermediate end point that correlates with disease progression but does not correlate with PSA changes adds power to the evaluation of a drug across the spectrum. Consider the following example. Tumor cells that express specific mutations in *c-kit* or which harbor a functionally active *c-kit* signaling pathway are highly sensitive to imatinib. Trials in patients with chronic myeloge-

nous leukemia and gastrointestinal stromal tumors established an effective dose of the drug that could be administered for a prolonged period of time. Subsequent work showed that tumors with an activated platelet derived growth factor receptor (PDGFr) signaling pathway might also be sensitive to the compound, including prostate cancers that have metastasized to bone [77], and by inference, localized prostate cancers that have been shown to overexpress PDGFr [78]. This provided a rationale for testing in prostate cancer. The initial trial of imatinib in prostate cancer evaluated patients with clinically metastatic castrate disease in bone, and included correlative studies seeking to confirm the presence of the receptor in bone metastases and changes in receptor levels after treatment. This was not only cumbersome for the patient and costly, but often the biopsy itself was negative for tumor.

Consequently, many groups have explored changes in normal tissues that are easier to obtain on a consistent basis for pharmacodynamic dosing. Tissues that have been used include peripheral blood mononuclear cells obtained by venipuncture, buccal mucosa smears, skin biopsies, or hair follicles. Changes that have been measured include inhibition of a particular signaling pathway or target protein, the induction of specific target proteins, and effects on proliferation. For the evaluation of imatinib, an assay that correlated dephosphorylated PDGFr in tumor with dephosphorylated PDGFr in a hair follicle, a specimen that is easily obtained with little patient discomfort, was developed. In a trial that includes patients with a rising PSA, if the dose explored is shown to affect PDGFr phosphorylation status and there is no effect on PSA, it is unlikely that the drug will be developed further as a single agent.

The situation may be different for immunologic approaches that affect circulating cells and not solid masses of tumor, or for approaches that in theory may have no effect against large tumor burdens. In this case, a failure to demonstrate an antitumor effect in late-stage disease may not predict for a lack of efficacy in minimal disease. Many immunotherapy trials have as their primary end point an immunologic measurement such as the induction of a specific antibody titer or measures of T-cell function. The issue is that few, if any, of these end points have been associated with an antitumor effect in prostate cancer or in any tumor type. As a result, the issue of dose is often unresolved, and the decision to discard or advance the approach is too often entirely empiric.

Treatment Effect

Trials designed to determine treatment effect, analogous to phase II trials in traditional drug development, are essential to assess whether to commit the human and financial resources necessary to conduct a definitive randomized trial using objective, non-PSA-based, clinical benefit end points. The situation is complicated further by the number

Table 5. Sequential Outcomes to Demonstrate Treatment Effects and Prioritize for Clinical Benefit Studies

Define intervention specific posttherapy PSA change
Determine the proportion who demonstrate the decline
Demonstrate the duration of effect on PSA and concurrently, on delay of metastatic progression
Ranking
Match eligibility profiles for risk of metastatic progression
Consider the proportion of patients remaining on study at each time point
Abbreviations: PSA, prostate-specific antigen.

of agents now available for testing. As such, these trials should also provide objective measures to prioritize drugs for definitive evaluation. Eligibility criteria should include patients with a predetermined risk of developing metastatic disease, or ideally with the expectation that patients with the same risk profile would be treated in the phase III study [79]. The level of risk was not defined.

An issue that affects the design and ability to complete both treatment effect and clinical benefit studies is whether early hormonal therapy prolongs life, and whether deferring hormones to explore an investigational approach would compromise a patient's overall outcome. International trends are to administer androgen ablation therapy earlier, on the basis of randomized trials showing a delay in progression along with a suggestion of a survival benefit when hormone therapy is used as an adjuvant (early) to local therapy rather than as a salvage (delayed) approach when relapses were documented [80-83]. This question has not been carefully incorporated in trial design. It was the consensus of the Group that the data were insufficient to recommend early immediate hormone therapy to all patients, and that given the adverse effects of these treatments, that trials that do not incorporate hormonal therapy were still acceptable. The issue of early versus delayed therapy is critical for patients in this clinical state.

The evaluation for treatment effects involves three components: defining an intervention-specific posttherapy PSA change could represent a change in the natural history; determining the proportion of treated patients who show the change; and measuring the proportion of patients who do not develop metastatic disease at different fixed time points.

There are many posttherapy PSA change definitions in use, and often, the favorable intervention-specific posttherapy PSA change that is defined seems arbitrary. These outcomes range from a decline in the absolute value, a decrease by a defined percentage, no change, a decline in slope, or an increase in doubling time. Alternatively, the proportion of patients who achieve an undetectable PSA can be studied. But whatever definition is used, the trial design should state the specific posttherapy PSA change that is considered favorable for the drug under study, along with the proportion of patients who achieve the end point that is required to advance the drug. For drugs that pass the initial hurdle, additional patients can be enrolled to begin to estimate the duration of effect. A one-, two-, or multistage statistical design that controls the alpha (type I) and beta (type II) error can be used.

Previous work in patients with castrate metastatic disease demonstrated that PSA changes represent only a small but significant predictor of a patient's survival [62,84]. Maintaining a low biochemical failure rate is a necessary but not a sufficient condition for a delay in objective disease progression and for prolonged survival in this population.

As such, measures of a treatment effect should not be based on PSA changes, but on a time-dependent parameter such as the time to development of detectable clinical metastatic disease, which requires that patients be evaluated at regular intervals with physical examinations, symptom assessments, and imaging studies. Demonstrations of a delay in time to progression with a nonhormonal approach is an indication that a regimen is worthy of testing using a survival end point.

When considering different outcomes, few would argue that a drug was having a biologic effect if a patient's PSA-DT were increased by a factor of 2. This change in PSA-DT is one example of an arbitrarily defined bar. The concern of a PSA end point that accepts any degree of rise from baseline as a favorable outcome is whether patients will remain on the study with a rising PSA until clinical metastases are observed. In practice, many patients receive androgen ablation or other therapy to alleviate the anxiety associated with a PSA that is continuing to rise [85]. In practice, the proportion of patients who remain on study without metastatic disease, the proportion who receive a secondary therapy before the end point of metastatic disease, and the proportion who develop metastatic disease should be recorded separately. Androgen ablation therapies lower PSA levels and delay metastatic progression [81], and the trial cannot be completed. As such, to show that the development of metastatic disease has been prevented or delayed, the defined posttherapy PSA change must be meaningful enough so that a patient will remain on the trial for a sufficient period of time. Examples are illustrated by Figures 2A to 2D and 2H. Patients who receive secondary therapies as a result of increasing PSA trajectory should continue to be observed for objective disease progression. In this way, an analysis for multiple possible failure types can be calculated, although the definitive end point remains time to development of metastatic disease. As noted previously, delaying time to metastatic disease is one justification for designing and prioritizing a trial using a survival-based end point.

The situation is different for agents that may be anticipated to influence prostate cancer growth independent of an effect on PSA. Agents that affect host-tumor interactions with no or a limited effect on the tumor itself (such as antiangiogenic agents, antimetastatic compounds, and those designed to minimize tumor seeding in bone) are some examples. Such agents may indeed have a role in management, but, because of the lack of an effect on PSA, it is unlikely that a study based on time to objective metastatic progression can be completed. The evaluation of these agents will require the incorporation of hormone therapy into the trial design, using time to treatment failure as the end point. In one example of such a design, patients are exposed to 3 months of hormonal therapy and then randomly assigned to receive or not receive the experimental

agent—in this case, an angiogenesis inhibitor. Sample size estimates can be based on predicted failure probability of placebo-treated patients that exceeds 90%. Recovery of testicular function and increasing testosterone levels, a powerful inducer of PSA expression and release, may confound the comparison. Although this is adjusted for in part by randomization, it is important to demonstrate that the levels of testosterone were comparable between the two groups at the time of analysis.

Multiarmed phase II trials can also be used to test different agents in a single trial. In this design, single or multiple experimental therapies are compared to a concurrent control- or standard-arm treatment. Different doses and schedules can also be studied. At the end of the treatment effect study, if the experimental treatment does not demonstrate a sufficient reduction in the objective disease progression rate relative to the control, the study is terminated.

Ranking. A prospective randomized trial is the most valid way to compare the results of different agents. Given the advances in discovery and the number of therapies now available for testing, some criteria to prioritize one therapy versus another for definitive testing will be essential. The proportion of patients who remain on study A and study B without metastases at a given time might be used to help assess which agents are worthy of study in a definitive clinical benefit trial. Critical to the ranking of agents is the enrollment of patients with similar probabilities of developing a clinically significant event. The latter has not been standardized. In addition, standard imaging to detect metastases must be performed at fixed intervals, recognizing that the PSA changes observed may not mirror overall disease status. Imaging should also be performed when a patient discontinues treatment for any reason. Table 2 illustrates the outcomes with two different treatment programs on the basis of percent change in PSA from baseline, the status of patients on the trial, and reasons for withdrawal. As shown, the first regimen produced short-term declines in PSA of greater than 50% in 5 of the 65 patients (8%) observed for 12 months, whereas many patients discontinued treatment because of a rising value. With the second regimen, the degree of decline was greater and more durable, with 25% of men showing continued declines at 24 months, and fewer patients showing objective metastatic progression. The lack of a treatment effect for regimen one relative to regimen two is also shown by the difference in the proportion of men showing objective metastatic progression.

Clinical Benefit

Prospective randomized comparisons provide the most definitive evidence of clinical benefit. The gold standard end point is overall survival. The proportion of patients who are alive at time x with no evidence of disease is a possible alternative for determining disease-free survival.

Survival-based end points are inefficient for patients with a rising PSA because many patients have long survival times independent of therapy. A survival-based end point is feasible for patients with a high risk of prostate cancer–specific death. As an alternative to survival, the Group accepted the time to the development of objective evidence of disease on an imaging or on physical examination, or the transition to clinically metastatic noncastrate disease as clinically beneficial. This is because it is the point in the illness where a patient is at risk for developing symptoms and of dying of prostate cancer [8]. Survival-based end points are possible for patients with high risk of death (ie, 5 years).

The Group also recognized that a patient could be considered to have benefited from treatment if symptoms were prevented, but that the end point was more difficult to prove in this patient population because symptoms only occur after metastatic progression has been demonstrated. Reducing the toxicities of or obviating the need for hormonal therapy would also be considered beneficial but will not be considered further. The more important factor relevant to completing these studies is the clinical reality that many do not remain on trial if PSA levels continue to increase. This reiterates the importance of a high bar for the results of treatment effect trials before a clinical benefit study is considered.

The clinical benefit end point should evolve directly from the treatment effect studies so that the trial can have high power with its sample size. The eligibility criteria with respect to the risk of developing a clinically significant event should also be the same. The exact level of risk of metastatic progression will vary for the type of intervention being proposed: the higher the risk, the more acceptable the toxicities. However, if eligibility criteria are such that only the highest-risk patients are selected, accrual may slow to levels that are not sustainable.

In conclusion, developing therapies for patients in the state of a rising PSA is challenging because it takes place in the absence of symptoms, radiographic findings, or pathologic correlates to determine treatment effects. The challenge is unavoidable, because the population with rising PSA now represents the second largest group of patients with prostate cancer. This Group agreed on a methodology to show whether a drug can favorably alter the natural history of the disease. It included the recognition that drug development would rarely begin testing in this patient group until the safety profile was established and there was preliminary evidence of efficacy in patients with more advanced disease. The Group also recognized the importance of refining prognostication and risk stratification on the basis of parameters in the primary tumor, clinical determinants, and PSA kinetics (eg, PSA-DT) that are critical to patient care. A wide range of new therapies are available for testing, from traditional cytotoxic drugs to novel agents that target specific pathways. There should be no

presumption that targets present in other clinical states, such as those with localized disease or castrate metastatic disease, are present in tumor cells from patients in the state of a rising PSA.

There was consensus that the clinical benefit of a treatment or approach could be demonstrated if trial entry was restricted to patients who needed to be treated, that testing was restricted to drugs worthy of evaluation, and that a high bar was set to move a drug or approach forward. Current data suggest that PSA-DT represents a powerful predictor of distant metastasis and disease-specific survival in this patient population. The evaluation should proceed in a sequence that defines an optimal dose and schedule; demonstrates a treatment effect; and demonstrates clinical benefit. PSA-based criteria for a treatment effect should be intervention specific, varying by the mechanism of the drug. A posttherapy PSA change is a short-term end point; absence of objective progression and survival are the long-term end points. The group concurred that treatment-induced changes in PSA do not necessarily mean that a patient has benefited from the therapy, and that the PSA level in and of itself should not be used as the sole treatment response. The Group also believed that the term PSA response should be abandoned. Nonetheless, the Group believed that posttherapy PSA changes can (and should) be used to detect drug activity. Agents that fail to affect PSA kinetics should be abandoned; those that have a favorable impact should be studied for treatment effects and clinical benefit using new radiographic findings as the end point. These data indicated that PSA-DT might be a surrogate for survival. Additional studies from well-controlled prospective studies are needed to confirm these results. At the same time, the search for additional markers must continue—in particular, those that are not modulated by hormonal therapy.

The Group recommended a method of reporting on the basis of a proportion of patients who show a defined change in PSA, the duration of the change, and the absence of metastatic disease at fixed time intervals after treatment. This will allow investigators to compare visually their results with results of other investigators and will assist in prioritizing agents for further evaluation. Innovative study designs focused on clinical benefit also represent a valuable method to assess the role of candidate biomarkers as intermediate end points for future studies.

The Group was unanimous in the belief that assessing quality of life in this cohort was essential, particularly when the morbidity of the therapy might outweigh the survival benefit and the therapy is administered early in the disease process. Traditional quality-of-life measurement via utility assessment was recommended. Measuring utilities would yield a quality-adjusted survival time metric, which could easily be used to compare treatments on the quantity and quality-of-life outcomes simultaneously. Alternatively, a sensitive measure of symptom frequency, intensity, and

duration could be used. In this context, symptom-induced distress, sense of well-being, and self-assessed quality of life could be evaluated.

Acknowledgment

We thank Gunnar Steineck for his critical review and thoughtful comments.

Appendix A: Summary of Recommendations

I. HYPOTHESIS

The clinical states framework can be used to focus drug development on trials specific to the state of a rising PSA. Conditions under which a favorable change in the natural history of the disease can be demonstrated include:

- a. The design of trials in a sequence in which the results of one study are used to develop subsequent trials.
- b. The identification of cohorts of men in whom the rising PSA is indicative of metastatic (nonlocal) progression who require an intervention based on a predetermined risk of developing metastatic disease.
- c. The recognition that the initial evaluation of compound or approach would rarely begin in this patient group until efficacy was demonstrated in more advanced disease and safety was established, unless the drug targeted a pathway, mutation, or determinant unique to this clinical state.
- d. That the outcomes of success or failure are tailored to the agent under evaluation.
- e. That the effect of the drug on PSA expression or secretion was understood as well as possible, and the timing of the change in PSA if the treatment is successful was anticipated.
- f. Avoiding the use of the term “PSA response” as evidence of an anticancer effect, because one set of criteria would not be applicable to all agents.
- g. The recognition that although PSA-based outcomes are useful to screen for a biologic effect, they are not a surrogate for clinical benefit. Demonstrating clinical benefit requires studies with non-PSA–based end points.
- h. To demonstrate a favorable effect on a non-PSA–based end point requires that only agents that produce no rise or a decline in PSA in a significant proportion of patients are moved forward. Agents that do not produce a decline or stabilization in PSA can only be studied in combination.

II. PATIENT POPULATION

The population of men enrolled onto trials should have experience failure of primary therapy, have a high likelihood of systemic disease, and a sufficient risk of a clinically significant event so that the potential for benefit outweighs the risks of study treatment. The probability of developing the event and the time in which it is estimated to occur remains to be defined.

a. Failure of primary therapy: A patient is considered to have progressed after a radical prostatectomy if the PSA is detectable 8 weeks or more after the procedure, and a subsequent value is rising. A patient is considered to have experienced treatment failure after radiation therapy if three consecutive rises in PSA with at least 2 years of follow-up after the start of radiation are documented, with the time of failure as the midpoint between the nadir and the first confirmed rise [20]. The so-called PSA bounce should be recognized and excluded.

b. High risk of systemic disease: There are no specific criteria that predict with certainty which patients in the state of a rising PSA after radical prostatectomy or radiation therapy have disease that is limited to the prostate bed or the prostate itself, who might benefit from additional local therapy. Factors that predict for a local as opposed to systemic recurrence are men with a low PSA (< 1 ng/mL), a long (> 1 year) time to failure, and a slow (> 1 year PSA-DT). With longer follow-up, PSA-DT has replaced prostatectomy Gleason score and time to PSA failure as predictors of metastatic progression. At a minimum, imaging with a bone scan and CT scan are recommended to exclude metastatic disease. Data were insufficient to make a recommendation regarding PET, transrectal ultrasound, MRI, or Prostatecint scans.

Clinical disease detected by digital rectal examination, MRI, or other imaging study should be confirmed by biopsy (at least 2 years after complete radiation therapy).

c. High risk of developing metastatic disease and prostate cancer–specific mortality: Models that define risk of developing metastatic disease and of a prostate cancer–specific death in a defined period of time are being developed. Evolving data suggest that the initial Gleason score and PSA doubling time may be most predictive.

d. Trial eligibility.

Baseline PSA value. By consensus, the Group suggested that enrollment onto a clinical trial require a PSA level that exceeds 0.4 ng/mL and is rising for a patient previously treated by surgery, and 1.5 ng/mL and rising for a patient treated with radiation therapy alone or in combination with hormonal therapy. This was proposed with the recognition that errors will occur with any cut point, but that as long as serial PSA measurements are obtained, and the elevations are confirmed, misinterpretations would be minimized.

PSA-DT. For the calculation of doubling time, a minimum of four PSA values was suggested. Data were insufficient to make a recommendation for a specific doubling time.

Baseline testosterone level: For patients who have received hormones, testosterone levels should be above 150 ng/dL or should have returned to the patient's pretreatment baseline.

III. INTERVENTION

The decision to test a compound or approach in this clinical state should consider the mechanism and target of

the approach, and the clinical experience to date. Most approaches are best evaluated in patients with more advanced disease before testing in patients with a rising PSA to ensure safety and obtain preliminary evidence of efficacy. There are exceptions. The investigator should anticipate the effect of the therapy on PSA using information derived from in vitro studies and/or xenograft model systems, although the utility and reliability of these assays has not been validated.

IV. OUTCOMES AND REPORTING

The reporting of the trial should include characteristics of the tumor at the time of diagnosis (eg, T stage and Gleason grade), the PSA level at diagnosis, details of prior therapies, the behavior of the PSA before study treatment begins, and the posttherapy PSA patterns while receiving treatment. The following guidelines were suggested:

Prior treatments: All prior therapies should be described, including the mode of local therapy (radiation *v* surgery *v* cryotherapy), neoadjuvant or adjuvant therapies administered, and the timing and mode of any salvage therapies. All other investigational therapies before the one currently under study should also be recorded, including the doses and duration of treatment.

Pretreatment PSA kinetics: Pretreatment PSA kinetics or PSA-DT should be described using as many values as possible, with a minimum of four values before the study. The optimal run-in time was not defined but a minimum of 6 months was suggested. To the extent possible, all PSA values should be analyzed at the same laboratory.

Posttherapy PSA: The posttherapy PSA change definition of interest, including the anticipated timing of the effect, will vary for drugs that act via different mechanism. The definition should consider results from in vitro and in vivo studies, and the clinical experience with the approach. The analysis of posttreatment PSA changes requires that there is no intercurrent use of androgen deprivation or other hormonal agents, PSA levels be measured at least once a month, and there are a minimum of three PSA values to evaluate after treatment. The outcomes can be reported as:

% change in PSA: The posttherapy change in PSA from baseline can be reported as an absolute percentage at any time or at a particular landmark time.

Changes in doubling time or slope: The posttherapy PSA-DT or slope can be reported over different time intervals, and compared with the pretreatment kinetics. The method of calculating doubling time, the number of data points, and the span over which they are recorded should also be reported.

Duration of effect: The duration of effect should be measured from the time the patient began treatment with the investigational therapy to the time of progression.

PSA-based definitions of disease progression: Progression of disease on the basis of PSA may be defined on the basis of an increase to a predetermined number, a change in

the postintervention rate of rise, or an increase by an absolute percentage. The definition used should be stated in the trial and consider the mechanism of the drug or agent under study. Difficulties arise when evaluating drugs that are designed to (reduce proliferation) slow the disease without killing cells, or drugs that require a prolonged exposure time to produce the desired effect on disease progression. A change in PSA slope may not be appropriate for a differentiating agent that often causes a rise in PSA before a decline, or for compounds designed to slow progression that may be beneficial despite continued rises in PSA.

Safety: Adverse events should be reported using National Cancer Institute Common Toxicity Criteria.

Clinical progression: There was a consensus that the detection of disease on physical examination or on imaging modality represents progression independent of the effects on PSA. Imaging studies to detect metastatic or local disease should be performed at fixed time intervals.

Change in therapy: Administration of a secondary therapy is considered treatment failure. It may be prescribed to alleviate the anxiety associated with PSA levels that are continuing to rise while the patient receives therapy even if the rate of rise has been slowed. In view of the significant patient and physician subjectivity involved in the decision to implement new therapy, the time and reasons for initiating the new therapy, be it hormones or other secondary treatment, should be recorded.

Reporting: For consistency, the Group recommended a report in a tabular format that records the number of patients who meet different PSA-based outcomes at defined posttreatment intervals (Table 2). The table includes the number of patients enrolled, and at fixed time points following therapy, and the number meeting specific PSA-based criteria. The number who continue to receive treatment and who have discontinued treatment are also recorded. The reason a patient was taken off study should also be recorded, be it the development of clinically detectable metastatic and/or local disease, adverse event, anxiety, or the administration of a different treatment for any reason. This approach allows a rapid visualization of the proportion of patients who have met a specific outcome criterion and who have not undergone a transition to a more advanced state.

V. TRIAL DESIGN

The decision to study a drug in this population should be based on the collective experience with the compound to date. A drug can be considered for development if it has shown a desired biologic effect in patients with more advanced clinical states, it has a meaningful biologic surrogate of activity that has been linked with efficacy in other tumor types, and/or it has an effect on a target pathway known to

contribute to the growth of prostate cancer and it has been given safely to normal volunteers. Clinical testing should rarely begin in this patient population. The phases of drug development for trials in this clinical state are dose and schedule, treatment effect, and clinical benefit.

a. **Dose and schedule:** In contrast to traditional phase I testing, a key issue is to optimize exposure to the drug for prolonged periods of time. More intensive dose/biologic effect studies are encouraged.

b. **Treatment effect:** In the initial screen for a biologic effect, a predetermined number of patients are enrolled and treated, and posttherapy change in PSA is assessed. The primary outcome that must be met to move the drug forward should be defined prospectively, and with the recognition that different decision rules will be needed for drugs of different mechanisms. The Group suggested a high bar that uses, at a minimum, no rise in PSA from baseline as the initial screen. Declines in PSA were preferred so that a large proportion of patients remain on study. Physical examinations and serial imaging with a bone scan and abdominal/pelvic CT scan at a minimum are recommended to ensure that there is no radiographic progression.

For drugs that pass the initial hurdle, additional patients can be enrolled to begin to estimate the duration of effect, and to begin to define cohorts of patients who might benefit. For quantitation of the duration of the effect, a time-dependent parameter should be set. This would include patients who showed objective progression, and those who went off study or received secondary therapies before reaching the end point of metastatic progression.

To test a drug that may affect prostate cancer growth independent of an effect on PSA will typically require the integration of hormone therapies in the trial design.

Ranking: An analysis of the proportion of patients who remain on study without metastases at a given time may be useful to assess which agents are worthy of study in a definitive phase III trial. To do so requires enrollment of patients with similar risk profiles for developing metastatic disease.

c. **Clinical benefit:** Clinical benefit trials should be designed directly from treatment effect studies. The patient populations should be matched for risk, and the magnitude of the treatment effect observed should determine how the clinical benefit study is powered. PSA-based end points were not considered definitive evidence of benefit, and although survival-based end points were preferred, the Group accepted the time to development of metastatic disease as an alternative. Quality of life should also be recorded.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Appendix B. Other Participants

Investigator	Institution David B. Agus, MD
Peter R. Carroll, MD	University of California, San Francisco, San Francisco, CA
William Dahut, MD	National Cancer Institute, Bethesda, MD
Nancy A. Dawson, MD	Greenebaum Cancer Center, University of Maryland, Baltimore, MD
Theo M. deReijke, MD	Academic Medical Center, Amsterdam, The Netherlands
William D. Figg, MD	National Cancer Institute, Bethesda, MD
Daniel George, MD	Dana-Farber Cancer Institute, Boston, MA
Eric A. Klein, MD	Cleveland Clinic, Cleveland, OH
Hans Lilja, MD, PhD	Memorial Sloan-Kettering Cancer Center, New York, NY
William G. Nelson, MD, PhD	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
Vicky Sinibaldi, RN	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
Leon Sun, MD, PhD	Uniformed Services University of the Health Science, Rockville, MD
Bruce Trock, MD	Johns Hopkins School of Medicine, Baltimore, MD
Robin T. Vollmer, MD	VA Medical Center, Durham, NC
Vivian Weinberg, PhD	University of California San Francisco, San Francisco, CA
Michael Zelefsky, MD	Memorial Sloan-Kettering Cancer Center, New York, NY

REFERENCES

- Jemal A, Thomas A, Murray T, et al: Cancer statistics, 2002. *CA Cancer J Clin* 52:23-47, 2002
- Svetec D, Thompson IM: PSA screening: Current controversy. *Ann Oncol* 9:1283-1288, 1998
- Dixon SC, Knopf KB, Figg WD: The control of prostate-specific antigen expression and gene regulation by pharmacological agents. *Pharmacol Rev* 53:73-91, 2001
- Denmeade SR, Sokoll LJ, Dalrymple S, et al: Dissociation between androgen responsiveness for malignant growth vs. expression of prostate specific differentiation markers PSA, hK2, and PSMA in human prostate cancer models. *Prostate* 54:249-257, 2003
- Moul JW: Prostate specific antigen only progression of prostate cancer. *J Urol* 163:1632-1642, 2000
- Vollmer RT, Humphrey PA: Tumor volume in prostate cancer and serum prostate-specific antigen: Analysis from a kinetic viewpoint. *Am J Clin Pathol* 119:80-89, 2003
- Pound CR, Partin AW, Eisenberger MA, et al: Natural history of progression to metastases and death from prostate cancer in men with PSA recurrence following radical prostatectomy. *JAMA* 281:1591-1597, 1999
- Scher HI, Heller G: Clinical states in prostate cancer: Towards a dynamic model of disease progression. *Urology* 55:323-327, 2000
- Fleming C, Wasson JH, Albertsen PC, et al: A decision analysis of alternative treatment strategies for clinically localized prostate cancer. *JAMA* 269:2650-2659, 1993
- Kattan MW, Stapleton AMF, Wheeler TM, et al: Evaluation of a nomogram for predicting pathological stage of men with clinically localized prostate cancer. *Cancer* 79:528-537, 1997
- Padula GD, Zelefsky MJ, Venkatraman ES, et al: Normalization of serum testosterone levels in patients treated with neoadjuvant hormonal therapy and three-dimensional conformal radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 52:439-443, 2002
- Gulley JL, Figg WD, Carter J, et al: A prospective analysis of the time to normalization of serum testosterone (T) following 6 months of androgen deprivation therapy in patients on a randomized phase III clinical trial utilizing intermittent hormonal therapy. *Proc Am Soc Clin Oncol* 22:396, 2003 (abstr 1592)
- Lukka H, Warde P, Pickles T, et al: Controversies in prostate cancer radiotherapy: Consensus development. *Can J Urol* 8:1314-1322, 2001
- Taylor JM, Griffith KA, Sandler HM: Definitions of biochemical failure in prostate cancer following radiation therapy. *Int J Radiat Oncol Biol Phys* 50:1212-1219, 2001
- Oesterling JE: Prostate specific antigen: A critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. *J Urol* 145:907-923, 1991
- Han M, Partin AW, Zahurak M, et al: Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. *J Urol* 169:517-523, 2003
- Gretzer MB, Trock BJ, Han M, et al: A critical analysis of the interpretation of biochemical failure in surgically treated patients using the American Society for Therapeutic Radiation and Oncology criteria. *J Urol* 168:1419-1422, 2002
- Amling CL, Bergstralh EJ, Blute ML, et al: Defining prostate specific antigen progression after radical prostatectomy: What is the most appropriate cut point?. *J Urol* 165:1146-1151, 2001
- Amling CL, Blute ML, Bergstralh EJ, et al: Defining biochemical progression after radical prostatectomy: What is appropriate PSA cut-point? *J Urol* 163:284, 2000 (suppl; abstr)
- Panel ASTRO: Consensus statement: Guidelines for PSA following radiation therapy. *Int J Radiat Oncol Biol Phys* 37:1035-1041, 1997
- Kattan MW, Zelefsky MJ, Kupelian PA, et al: Pretreatment nomogram for predicting the outcome of three-dimensional conformal radiotherapy in prostate cancer. *J Clin Oncol* 18:3352-3359, 2000
- Critz FA, Levinson AK, Williams WH, et al: Prostate-specific antigen nadir: The optimal level after irradiation for prostate cancer. *J Clin Oncol* 14:2893-2900, 1996
- Taplin ME: Biochemical (PSA) relapse in prostate cancer. *PPO Updates* 17:1-14, 2003
- Critz FA, Williams WH, Benton JB, et al: Prostate specific antigen bounce after radioactive seed implantation followed by external beam radiation for prostate cancer. *J Urol* 163:1085-1089, 2000
- Hanlon AL, Pinover WH, Horwitz EM, et al: Patterns and fate of PSA bouncing following 3D-CRT. *Int J Radiat Oncol Biol Phys* 50:845-849, 2001
- Das P, Chen MH, Valentine K, et al: Using the magnitude of PSA bounce after MRI-guided prostate brachytherapy to distinguish recurrence, benign precipitating factors, and idiopathic bounce. *Int J Radiat Oncol Biol Phys* 54:698-702, 2002
- Ballentine Carter H, Morrell CH, Pearson JD, et al: Estimation of prostatic growth using serial prostate-specific antigen measurements in men with and without prostatic disease. *Cancer Res* 52:3323-3328, 1992
- Patel A, Dorey F, Franklin J, et al: Recurrence patterns after radical retropubic prostatectomy: Clinical utility of PSA doubling times and log slope PSA (prostate specific antigen). *J Urol* 158:1441-1445, 1997
- DiPaola RS, Zhang H, Lambert GH, et al: Clinical and biologic activity of an estrogenic herbal combination (PC-SPES) in prostate cancer. *N Engl J Med* 339:785-791, 1998
- Leventis AK, Shariat SF, Kattan MW, et al: Prediction of response to salvage radiation therapy in patients with prostate cancer recurrence after radical prostatectomy. *J Clin Oncol* 19:1030-1039, 2001
- Laufer M, Pound CR, Carducci MA, et al: Management of patients with rising prostate-specific antigen after radical prostatectomy. *Urology* 55:309-315, 2000
- Moul JW, Kane CJ, Malkowicz SB: The role of imaging studies and molecular markers for selecting candidates for radical prostatectomy. *Urol Clin North Am* 28:459-472, 2001

33. Cher ML, Bianco FJ Jr, Lam JS, et al: Limited role of radionuclide bone scintigraphy in patients with prostate specific antigen elevations after radical prostatectomy. *J Urol* 160:1387-1391, 1998
34. Sella T, Schwartz LH, Swindle PW, et al: Endorectal coil MR in patients with suspected local recurrence following prostatectomy. *Am J Radiol* (in press)
35. Goldenberg SL, Carter M, Dashefsky S, et al: Sonographic characteristics of the urethrovesical anastomosis in the early post-radical prostatectomy patient. *J Urol* 147:1307-1309, 1992
36. Connolly JA, Shinohara K, Presti JC Jr, et al: Local recurrence after radical prostatectomy: Characteristics in size, location, and relationship to prostate-specific antigen and surgical margins. *Urology* 47:225-231, 1996
37. Kao CH, Hsieh JF, Tsai SC, et al: Comparison and discrepancy of 18F-2-deoxyglucose positron emission tomography and Tc-99m MDP bone scan to detect bone metastases. *Anticancer Res* 20:2189-2192, 2000
38. Sartor O, McLeod D: Indium-111-capromab pentetide scans: An important test relevant to clinical decision making. *Urology* 57:399-401, 2001
39. Hinkle GH, Burgers JK, Neal CE, et al: Multicenter radioimmunoscintigraphic evaluation of patients with prostate carcinoma using indium-111 capromab pentetide. *Cancer* 83:739-747, 1998
40. Holmes EH: PSMA specific antibodies and their diagnostic and therapeutic use. *Expert Opin Investig Drugs* 10:511-519, 2001
41. Izawa JI, Madsen LT, Scott SM, et al: Salvage cryotherapy for recurrent prostate cancer after radiotherapy: Variables affecting patient outcome. *J Clin Oncol* 20:2664-2671, 2002
42. Beyer D: Permanent brachytherapy as salvage treatment for recurrent prostate cancer. *Urology* 53:2-10, 1999
43. Zelefsky MJ, Leibel SA, Gaudin PB, et al: Dose escalation with three dimensional conformal radiation therapy affects the outcome in prostate cancer. *Int J Radiat Oncol Biol Phys* 41:491-500, 1998
44. D'Amico AV, Whittington R, Malkowicz SB, et al: Biochemical outcome after radical prostatectomy, external beam radiation therapy of interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 280:969-974, 1998
45. Moul JW, Connelly RR, Lubeck DP, et al: Predicting risk of prostate specific antigen recurrence after radical prostatectomy with the Center for Prostate Disease Research and Cancer of the Prostate Strategic Urologic Research Endeavor databases. *J Urol* 166:1322-1327, 2001
46. Partin AW, Yoo J, Ballentine Carter H, et al: The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. *J Urol* 150:110-114, 1993
47. Roach M III: Re: The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. *J Urol* 150:1923-1924, 1993
48. Roach M III: You say either, I say either, but let's not call the whole thing off: Models for predicting the risk of lymph node involvement in patients with prostate cancer. *Int J Radiat Oncol Biol Phys* 34:749-751, 1996
49. Roach M, Lu J, Pilepich MV, et al: Four prognostic groups predict long-term survival from prostate cancer following radiotherapy alone on Radiation Therapy Oncology Group clinical trials. *Int J Radiat Oncol Biol Phys* 47:609-615, 2000
50. Vollmer RT, Humphrey PA: The relative importance of anatomic and PSA factors to outcomes after radical prostatectomy for prostate cancer. *Am J Clin Pathol* 116:864-870, 2001
51. D'Amico AV, Moul J, Carroll PR, et al: Vital statistics following surgery or radiation for patients with clinically localized prostate cancer managed during the PSA era. *Proc Am Soc Clin Oncol* 22:381, 2003 (abstr 1528)
52. Sandler HM, Pajak TF, Hanks GE, et al: Can biochemical failure (ASTRO definition) be used as a surrogate endpoint for prostate cancer survival in phase III localized prostate cancer clinical trials? *Proc Am Soc Clin Oncol* 22:381, 2003 (abstr 1529)
53. Katz MS, Zelefsky MJ, Venkatraman ES, et al: Predictors of biochemical outcome with salvage conformal radiotherapy after radical prostatectomy for prostate cancer. *J Clin Oncol* 21:483-489, 2003
54. Stephenson AJ, Shariat SF, Kattan MW, et al: Predicting the outcome of salvage radiotherapy for suspected local recurrence of prostate cancer after radical prostatectomy. *Proc Am Soc Clin Oncol* 22:392, 2003 (abstr 1577)
55. Eisenberger MA, Partin AW, Pound C, et al: Natural history of progression of patients with biochemical (PSA) relapse following radical prostatectomy: Update. *Proc Am Soc Clin Oncol* 22:380, 2003 (abstr 1527)
56. Roberts SG, Blute ML, Bergstralh EJ, et al: PSA doubling time as a predictor of clinical progression after biochemical failure following radical prostatectomy for prostate cancer. *Mayo Clin Proc* 76:576-581, 2001
57. Kwan WB, Pickles T, Paltiel C: Does PSA failure in prostate cancer patients necessarily increase the risk of prostate cancer related death: An analysis in a cohort of 1790 patients. *Proc Am Soc Clin Oncol* 22:380, 2003 (abstr 1526)
58. Lee WR, Hanks GE, Hanlon A: Increasing prostate-specific antigen profile following definitive radiation therapy for localized prostate cancer: Clinical observations. *J Clin Oncol* 15:230-238, 1997
59. Zagars GK, Pollack A: Kinetics of serum prostate-specific antigen after external beam radiation for clinically localized prostate cancer. *Radiother Oncol* 44:213-221, 1997
60. Sandler HM, Dunn RL, McLaughlin W, et al: Overall survival after prostate-specific-antigen-detected recurrence following conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 48:629-633, 2000
61. D'Amico AV, Cote K, Loffredo M, et al: Determinants of prostate cancer-specific survival after radiation therapy for patients with clinically localized prostate cancer. *J Clin Oncol* 20:4567-4573, 2002
62. D'Amico AV, Moul JW, Carroll PR, et al: Vital statistics following surgery or radiation for patients with clinically localized prostate cancer managed during the PSA era. *Proc Am Soc Clin Oncol* 39, 2003
63. D'Amico AV, Moul JW, Carroll PR, et al: Cancer specific mortality following surgery or radiation for patients with clinically localized prostate cancer managed during the PSA era. *J Natl Cancer Inst* 95:1376-1383, 2003
64. Bubley GJ, Carducci M, Dahut W, et al: Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: Recommendations from the PSA Working Group. *J Clin Oncol* 17:3461-3467, 1999
65. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 92:205-216, 2000
66. Kelly WK, Scher HI, Mazumdar M, et al: Prostate specific antigen as a measure of disease outcome in hormone-refractory prostatic cancer. *J Clin Oncol* 11:607-615, 1993
67. Kelly WK, Osman I, Reuter VE, et al: The development of biologic end points in patients treated with differentiated agents: An experience of retinoids in prostate cancer. *Clin Cancer Res* 6:838-846, 2000
68. Scher HI, Mazumdar M, Kelly WK: Clinical trials in relapsed prostate cancer: Defining the target. *J Natl Cancer Inst* 88:1623-1634, 1996
69. Saad R, Bukowski RM, Lipton A, et al: Zoledronic acid is effective in preventing and delaying skeletal events in patients with bone metastases secondary to prostate and renal cancer. *Proc Am Soc Clin Oncol* 22:379, 2003 (abstr 1523)
70. Moertel CG, Fleming TR, Macdonald JS, et al: Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 322:352-358, 1990
71. The Ludwig Breast Cancer Study Group. Combination adjuvant chemotherapy for node-positive breast cancer. *N Engl J Med* 319:677-683, 1988
72. Thalmann GN, Sikes RA, Chang S-M, et al: Suramin-induced decrease in prostate-specific antigen expression with no effect on tumor growth in the LNCaP model of human prostate cancer. *J Natl Cancer Inst* 88:794-801, 1996
73. Solit DB, Zheng FF, Drobnjak M, et al: 17-Allylamino-17-demethoxygeldanamycin induces the degradation of androgen receptor and HER-2/neu and inhibits the growth of prostate cancer xenografts. *Clin Cancer Res* 8:986-993, 2002
74. Agus DB, Golde DW, Sgouros G, et al: Positron emission tomography of a human prostate cancer xenograft: The association of changes in deoxyglucose accumulation and response to hormonal therapy. *Cancer Res* 58:3009-3014, 1998
75. Scher HI: HER2 in prostate cancer: A viable target or innocent bystander? *J Natl Cancer Inst* 92:1866-1868, 2000
76. Scher HI: Prostate cancer: Defining therapeutic objectives and improving overall outcomes. *Cancer* 97(suppl 3):758-771, 2003
77. Uehara H, Kim SJ, Karashima T, et al: Effects of blocking platelet-derived growth factor-receptor signaling in a mouse model of ex-

perimental prostate cancer bone metastases. *J Natl Cancer Inst* 95:458-470, 2003

78. Singh D, Febbo PG, Ross K, et al: Gene expression correlates of clinical prostate cancer behavior. *Cancer Cell* 1:203-209, 2002

79. Fazzari M, Heller G, Scher HI: The phase II/III transition (phase IIb): Toward the proof of efficacy in cancer clinical trials. *Control Clin Trials* 21:360-368, 2000

80. Bolla M, Gonzalez D, Warde P, et al: Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 337:295-300, 1997

81. Messing EM, Manola J, Sarosdy M, et al: Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *N Engl J Med* 341:1781-1788, 1999

82. Pilepich MV, Caplan R, Byhardt RW, et al: Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: Report of Radiation Therapy Oncology Group Protocol 85-31. *J Clin Oncol* 15:1013-1021, 1997

83. See WA, Wirth MP, McLeod DG, et al: Bicalutamide as immediate therapy either alone or as adjuvant to standard care of patients with localized or locally advanced prostate cancer: First analysis of the early prostate cancer program. *J Urol* 168:429-435, 2002

84. Verbel DA, Heller G, Kelly WK, et al: Quantifying the amount of variation in survival explained by PSA. *Clin Cancer Res* 8:2576-2579, 2002

85. Roth AJ, Kornblith AB, Batel-Copel L, et al: Rapid screening for psychological distress in men with prostate cancer: A pilot study. *Cancer* 82:1904-1908, 1998