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Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group

Howard I. Scher, **Susan Halabi**, **Ian Tannock**, **Michael Morris**, **Cora N. Sternberg**, **Michael A. Carducci**, **Mario A. Eisenberger**, **Celestia Higano**, **Glenn J. Bubley**, **Robert Dreicer**, **Daniel Petrylak**, **Philip Kantoff**, **Ethan Basch**, **William Kevin Kelly**, **William D. Figg**, **Eric J. Small**, **Tomasz M. Beer**, **George Wilding**, **Alison Martin**, and **Maha Hussain**
Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, New York, NY; Duke University Medical Center, Durham, NC; Princess Margaret Hospital, Toronto, Ontario, Canada; Sam Camillo Forlanini Hospital, Rome, Italy; Beth Israel Deaconess Medical Center; Dana-Farber Cancer Center, Boston, MA; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore; National Cancer Institute, Bethesda,

Corresponding author: Howard I. Scher, MD, Genitourinary Oncology Service, Department of Medicine, Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10065; byczekb@mskcc.org.

AUTHOR CONTRIBUTIONS

Conception and design: Howard I. Scher, Susan Halabi, Ian Tannock, Michael Morris, Cora N. Sternberg, Michael A. Carducci, Mario A. Eisenberger, Celestia Higano, Glenn J. Bubley, Robert Dreicer, Daniel Petrylak, Philip Kantoff, Ethan Basch, William D. Figg, Eric J. Small, Alison Martin, Maha Hussain

Provision of study materials or patients: Howard I. Scher

Collection and assembly of data: Howard I. Scher, Mario A. Eisenberger, Celestia Higano, Tomasz M. Beer, Alison Martin

Data analysis and interpretation: Howard I. Scher, Michael Morris, Michael A. Carducci, Mario A. Eisenberger, Glenn J. Bubley, Robert Dreicer, Philip Kantoff, William Kevin Kelly, William D. Figg, Tomasz M. Beer, George Wilding, Alison Martin, Susan Halabi, Maha Hussain

Manuscript writing: Howard I. Scher, Susan Halabi, Ian Tannock, Michael Morris, Cora N. Sternberg, Michael A. Carducci, Mario A. Eisenberger, Celestia Higano, Glenn J. Bubley, Robert Dreicer, Ethan Basch, William Kevin Kelly, William D. Figg, Eric J. Small, Tomasz M. Beer, Alison Martin, Maha Hussain

Final approval of manuscript: Howard I. Scher, Susan Halabi, Ian Tannock, Cora N. Sternberg, Michael A. Carducci, Mario A. Eisenberger, Celestia Higano, Glenn J. Bubley, Robert Dreicer, Daniel Petrylak, Philip Kantoff, Ethan Basch, William Kevin Kelly, William D. Figg, Eric J. Small, Tomasz M. Beer, George Wilding, Alison Martin, Maha Hussain

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MD; University of Washington, Seattle, WA; Cleveland Clinic, Cleveland, OH; Columbia Presbyterian Medical Center, New York, NY; Yale Cancer Center, New Haven, CT; UCSF Comprehensive Cancer Center, San Francisco, CA; Oregon Health and Science Universeity, Portland, OR; University of Wisconsin Comprehensive Cancer Center, Madison, WI; and University of Michigan Comprehensive Cancer Center, Ann Arbor, MI

Abstract

Purpose—To update eligibility and outcome measures in trials that evaluate systemic treatment for patients with progressive prostate cancer and castrate levels of testosterone.

Methods—A committee of investigators experienced in conducting trials for prostate cancer defined new consensus criteria by reviewing previous criteria, Response Evaluation Criteria in Solid Tumors (RECIST), and emerging trial data.

Results—The Prostate Cancer Clinical Trials Working Group (PCWG2) recommends a two-objective paradigm: (1) controlling, relieving, or eliminating disease manifestations that are present when treatment is initiated and (2) preventing or delaying disease manifestations expected to occur. Prostate cancers progressing despite castrate levels of testosterone are considered castration resistant and not hormone refractory. Eligibility is defined using standard disease assessments to authenticate disease progression, prior treatment, distinct clinical subtypes, and predictive models. Outcomes are reported independently for prostate-specific antigen (PSA), imaging, and clinical measures, avoiding grouped categorizations such as complete or partial response. In most trials, early changes in PSA and/or pain are not acted on without other evidence of disease progression, and treatment should be continued for at least 12 weeks to ensure adequate drug exposure. Bone scans are reported as “new lesions” or “no new lesions,” changes in soft-tissue disease assessed by RECIST, and pain using validated scales. Defining eligibility for prevent/delay end points requires attention to estimated event frequency and/or random assignment to a control group.

Conclusion—PCWG2 recommends increasing emphasis on time-to-event end points (ie, failure to progress) as decision aids in proceeding from phase II to phase III trials. Recommendations will evolve as data are generated on the utility of intermediate end points to predict clinical benefit.

INTRODUCTION

Evaluating drugs to treat prostate cancer poses unique challenges. Measurable disease occurs infrequently, the natural history may be prolonged over decades, and because the treatment population is elderly, pursuing aggressive therapies may cause more harm than good. In 1999, the Prostate-Specific Antigen Working Group (PCWG1) addressed these challenges in their consensus recommendations for the conduct of clinical trials.[1] They focused on trial development for patients with metastatic prostate cancer whose disease was progressing despite castrate levels of testosterone and defined eligibility and outcome measures based on clinically relevant end points, and proposed standards for the use of prostate-specific antigen (PSA). In 2000, a broader collective of cancer researchers introduced New Guidelines to Evaluate the Response to Treatment in Solid Tumors (Response Evaluation Criteria in Solid Tumors [RECIST]).[2] This international initiative sought to standardize criteria to assess tumor response in trials for all solid tumors. Although

RECIST served some cancer swell, its metrics did not capture some key characteristics of prostate cancer.[3] For example, post-therapy changes in PSA, a routinely reported outcome in prostate cancer clinical trials and the primary focus of PCWG1, were not addressed by RECIST. In fact, none of the approved treatments for patients with prostate cancer would be available if trial outcomes were based solely on either the PCWG1 criteria or RECIST.

Since these two initiatives were introduced, the biology and natural history of prostate cancer have become better understood, and diverse new therapies, including bone-targeted agents and signaling inhibitors, have become available for clinical testing. In 2004, the US Food and Drug Administration (FDA) challenged the prostate cancer clinical trials community to rework the eligibility and outcome measures from PCWG1 so they could be applied across the clinical spectrum of the disease. The subsequent process prompted the formation of the Prostate Cancer Clinical Trials Working Group (PCWG2), a collective of international investigators who developed this report through meetings and electronic communication.

This article addresses clinical trials for patients with progressive prostate cancer despite castrate levels of testosterone and frames clinical trial questions for agents that act by diverse mechanisms. The consensus is that researchers should adopt a paradigm in which trial objectives are defined on the basis of controlling, relieving, or eliminating disease manifestations that are present when treatment is initiated, and/or of preventing or delaying disease manifestations expected to occur. This new paradigm expands the focus of prostate cancer clinical trials from traditional outcome measures such as early changes in PSA to time-to-event end points that capture the impact of treatment on important clinical manifestations and indicate when a drug should be stopped as the measure of antitumor effect. It also recommends standardized criteria for assessing patients. A goal of these recommendations is to ensure that a drug is not discontinued because of inappropriate outcome measures before it has had a chance to work.

Although the intent of these guidelines is to maximize the ability of phase II trials to screen or select promising therapies, the eligibility and outcome measures have broad applicability and are relevant to the design and conduct of phase III trials. Incorporation of similar parameters into phase III trials assessing overall survival is encouraged to generate the databases that will allow validation or refinement of the intermediate end points proposed herein.

I. CONCEPTUALIZING THE DISEASE

Investigators need to adopt a common language to categorize the clinical spectrum of prostate cancer from diagnosis to metastasis. When PCWG1 was published, no common vocabulary was broadly accepted. PCWG2 categorizes the disease continuum of prostate cancer on the basis of whether metastases are detectable (clinically or by imaging) and whether the serum testosterone level is in the castrate range by a surgical orchiectomy or medical therapy (Fig 1).[3,4] Each state on this continuum represents a scenario encountered routinely in clinical practice.

The clinical-states model identifies patients with distinct prognoses who might benefit (or not) from specific therapeutic approaches. The rising PSA states (castrate and noncastrate) signify that no detectable metastatic disease was found in the past or is now present. The clinical metastases states (castrate and noncastrate) signify that disease was detectable at some point in the past, regardless of whether it is detectable now. Along this disease continuum, a patient can only advance. For example, a patient with radiographically evident bone metastases at diagnosis would be assigned to the clinical metastases–noncastrate disease state. If that patient is treated with androgen depletion, no longer has radiographically evident disease, and has a PSA level that is not rising, he remains categorized in the clinical metastases–noncastrate state.

II. DEFINING THERAPEUTIC OBJECTIVES

Since the publication of PCWG1 criteria, clinical investigators have used them to define the primary end points for phase II trials for prostate cancer patients with progressive, castration-resistant disease. These trials are designed to demonstrate whether the therapeutic effects observed justify further evaluation in large-scale phase III trials. Phase III trials characterize the risk/benefit profile of the treatment in relation to either a placebo or established standards, such as time to clinically relevant progression, survival, or quality of life. The clinical-states model offers investigators a framework to standardize phase II end points to appropriately inform phase III end points.

PCWG2 distinguishes two types of phase II trial objectives: (1) those based on controlling, relieving, or eliminating disease manifestations that are present when treatment is initiated, and (2) those based on preventing or delaying future disease manifestations. Traditional measures of response reflect when a treatment is working; measures of progression indicate when a drug should be stopped. Because of the uncertainties associated with assessing response in bone and the controversy surrounding the clinical significance of post-therapy changes in PSA, PCWG2 recommends expanding the focus of phase II trials from measures of response to measures of progression. For most agents, a reliably determined, clinically relevant improvement in time to progression provides the most useful way to assess whether to proceed from a phase II to a phase III trial and may, if reproduced in a randomized, controlled trial, be evidence of clinical benefit from a regulatory perspective.

The drug evaluation pathways for cytotoxic and noncytotoxic agents need to be developed separately. Cytotoxic drugs typically produce a decline in PSA and regression of target lesions, whereas agents that act to slow tumor growth, inhibit destruction of bone, or inhibit angiogenesis may not. For example, a bone-directed therapy may prevent disease-related complications in the skeleton without influencing the growth of soft-tissue disease. Depending on the agent and the study, PCWG2 recommends that the effects of cytotoxic drugs be assessed with both control/relieve/eliminate or prevent/delay end points, and noncytotoxic drugs with prevent/delay end points.

Changes in existing manifestations of disease provide signals whether or not a treatment has produced an antitumor effect at an early stage, even though such changes may not necessarily signify clinical benefit. For example, a declining PSA level may be useful to

screen for the activity of a cytotoxic agent, even though it does not mean that the patient will live longer. However, when designing trials with control, relieve, or eliminate end points for patients with symptoms, it is often difficult to distinguish whether a symptom is related to the cancer, prior treatment, comorbidities, or a combination of factors.

Patients who lack discernible disease manifestations (eg, symptomatic bone pain), may be enrolled onto trials with prevent or delay end points that seek to prevent symptoms from occurring in the future. Manifestations that may occur in the future include growth at an existing site of disease, spread to additional sites, an increase in markers, new disease-related symptoms (eg, pain or other skeletal events), and death resulting from disease. The success of trials evaluating prevent or delay end points depends on the ability to define a patient cohort with a defined probability of developing the manifestations that the treatment is designed to prevent and in what time frame. Biases in interpreting the significance of time-to-event end points in phase II trials have been well described and support the case for randomized trial designs.[5] Regardless of the end point, it is essential that the trial be designed in a way that does not allow a drug to be discontinued prematurely on the basis of criteria that do not reflect that the treatment was ineffective or failed to benefit the patient.

III. ESTABLISHING ELIGIBILITY FOR ENROLLMENT

After defining the primary end points of efficacy (either control/relieve/eliminate or prevent/delay), investigators can effectively set eligibility criteria. PCWG1 restricted enrollment in trials to patients with progressive disease despite castrate levels of testosterone, based on changes in PSA, measurable disease, and bone scan, while controlling for antiandrogen withdrawal responses to avoid the potential erroneous misattribution of response to a study agent. PCWG2 modifies these eligibility criteria by authenticating disease with standardized assessments, considering the prior treatment history in more detail, defining distinct clinical subtypes, and highlighting the importance of predictive models for future clinical events.

The demonstration of a survival benefit in a phase III trial and a confirmatory trial[7] led to the approval of docetaxel in 2004.[6] Since then, clinical trials for patients with castrate metastatic disease are being designed in three contexts: before receiving treatment with docetaxel, with agents in combination with docetaxel to improve first-line outcomes, and as second-line treatment for patients with disease that has progressed despite docetaxel. Independent of the context, PCWG2 recommends defining therapeutic objectives in relation to the mechanism of action of the agent under study, documenting disease manifestations at the time treatment is started (Table 1), and serially evaluating patients post-treatment using standard assessments that relate to the objectives of the trial.

Authenticating Disease Progression

Authenticating disease progression is achieved by establishing standard pretreatment assessments and identifying standard criteria for disease progression for entry.

Pretreatment assessments—PCWG1 did not define a standard pretreatment evaluation, so PCWG2 builds on the standards for base-line evaluations recommended by RECIST and provides guidelines for imaging and symptom assessment.

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