NIH Public Access
Author Manuscript
Eur Urol. Author manuscript; available in PMC 2010 August 1.

Published in final edited form as:
Eur Urol. 2009 August ; 56(2): 237–244. doi:10.1016/j.eururo.2009.03.073.

Phase 1 Trial of High-Dose Exogenous Testosterone in Patients with Castration-Resistant Metastatic Prostate Cancer

Michael J. Morris[a,b,*], **Daisy Huang**[b], **William K. Kelly**[a,b], **Susan F. Slovin**[a,b], **Ryan D. Stephenson**[a], **Caitlin Eicher**[a], **Anthony Delacruz**[a], **Tracy Curley**[a], **Lawrence Schwartz**[c], and **Howard I. Scher**[a,b]

[a] Genitourinary Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

[b] Weill Medical College of Cornell University, New York, NY, USA

[c] Department of Radiology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Abstract

Background—Growth of selected castration-resistant prostate cancer (CRPC) cell lines and animal models can be repressed by reexposure to androgens. Low doses of androgens, however, can stimulate tumor growth.

Objective—We performed a phase 1 clinical trial to determine the safety of high-dose exogenous testosterone in patients with castration-resistant metastatic prostate cancer (CRMPC).

Design, setting, and participants—Patients with progressive CRMPC who had been castrate for at least 1 yr received three times the standard replacement dose of transdermal testosterone.

Intervention—Cohorts of 3–6 patients received testosterone for 1 wk, 1 mo, or until disease progression.

* Corresponding author. Genitourinary Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 444, New York, NY 10021, USA. Tel.: 646-422-4469; Fax: 212-988-0701. E-mail address: morrism@mskcc.org (M. J. Morris).

Author contributions: Michael J. Morris had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Morris, Kelly
Acquisition of data: Morris, Kelly, Slovin, Delacruz, Curley, Schwartz, Scher
Analysis and interpretation of data: Morris, Huang, Kelly, Slovin, Stephenson, Delacruz, Curley, Schwartz, Scher
Drafting of the manuscript: Morris, Huang, Stephenson
Critical revision of the manuscript for important intellectual content: Morris, Huang, Kelly, Slovin, Stephenson, Delacruz, Curley, Schwartz, Scher
Statistical analysis: Morris
Obtaining funding: Morris, Scher
Administrative, technical, or material support: Morris
Supervision: Morris
Other (specify): none

Trial registration: ClinicalTrials.gov; NCT00006044.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: none.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Measurements—Toxicities, androgen levels, prostate-specific antigen (PSA) assays, computed tomography (CT) scans, bone scintigraphy, positron emission tomography (PET) scans, and metastatic tumor biopsy androgen receptor levels were assessed.

Results and limitations—Twelve patients were treated—three in cohorts 1 and 2 and six in cohort 3. No pain flares were noted. One patient came off study because of epidural disease, which was treated with radiation. Average testosterone levels were within normal limits, although dihydrotestosterone (DHT) levels were supraphysiologic in cohort 3. One patient achieved a PSA decline of >50% from baseline. No objective responses were seen. For cohort 3, median time on treatment was 84 d (range: 23–247 d).

Conclusions—We have demonstrated that patients with CRMPC can be safely treated in clinical trials using high-dose exogenous testosterone. Patients did not, on average, achieve sustained supraphysiologic serum testosterone levels. Future studies should employ strategies to maximize testosterone serum levels, use contemporary methods of identifying patients with androgen receptor overexpression, and utilize PSA Working Group II Consensus Criteria clinical trial end points.

Keywords

Exogenous testosterone; Phase 1 trials; Prostate cancer

1. Introduction

Since the late 1940s, the standard treatment for metastatic prostate cancer (PCa) has been medical or surgical castration [1,2]. Even after patients progress following primary castrating hormonal therapies, secondary or tertiary hormones, or chemotherapy, most still receive androgen-lowering agents. The assumption is that rising testosterone levels stimulate tumor growth, since the androgen receptor remains functional even in castration-resistant patients.

Preclinical data, however, suggest that in select circumstances, there may be a role for testosterone repletion, even in the setting of castration-resistant disease. Androgen-independent cell lines, derived by raising LNCaP and others in androgen-depleted media for several generations, demonstrate growth repression when treated with supraphysiologic levels of exogenous, high-affinity androgens. Growth of these cells, characterized by androgen receptor (AR) overexpression and gene amplification, is inhibited by synthetic androgens at concentrations ≥0.1 nM (normal male testosterone levels: 10–35 nM) [3–6]. Animal models have demonstrated tumor necrosis and regression with testosterone supplementation [7]. Paradoxically, growth can be promoted by androgens at lower concentrations [3,4,8].

Early experiences using testosterone supplementation at Memorial Sloan-Kettering Cancer Center (MSKCC) between 1949 and 1967 resulted in adverse outcomes, including rapid progression. In those analyses, 45 of 52 evaluable patients appeared to suffer with added testosterone. These patients represented mixed clinical states: hormone naïve, castration sensitive, and castration resistant. The latter patients fared the worst, with 94% suffering ill effects from treatment [9]. In separate studies using androgen priming prior to chemotherapy, survival and other clinical outcomes were lower than in patients receiving chemotherapy alone [10,11]. Reports of benefit, particularly in castration-resistant patients, have been isolated and anecdotal [12].

We sought to test whether exogenous testosterone might be safely investigated in a manner that mirrors the successful preclinical data by treating a uniform group of patients with long-term castration-resistant metastatic disease using exogenous androgen at concentrations above an as-yet-unknown threshold of activity. We performed a phase 1 trial to test this hypothesis.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

2. Patients and methods

2.1. Eligibility criteria

Patients were >18 yr of age and signed their informed consent. The trial was approved by the institutional review board of MSKCC. Eligible patients had histologically confirmed PCa, which had become progressive, metastatic, and castration resistant. Radiographic progression was defined by World Health Organization (WHO) criteria [13]; new osseous lesions were determined by bone scintigraphy. Biochemical progression was defined as a 25% increase in prostate-specific antigen (PSA) over three tests. Patients were required to be castrated by orchiectomy or by gonadotropin-releasing hormone (GnRH) analogues for a minimum of 1 yr and were required to continue GnRH analogues during treatment if these were their form of castrating therapy. Patients could not receive other anticancer treatments within a month of treatment. Entry was also contingent on a serum testosterone <30 ng/ml, white blood cell count >3500/mm^3, platelet count >100 000/mm^3, bilirubin <2.0 mg/dl, creatinine <2.0 mg/dl or creatinine clearance >60 ml/min, and prothrombin time <14.5 s.

2.2. Treatment

Because preclinical data suggest that high levels of testosterone might arrest growth while lower doses could induce tumor flare, all patients received three times the standard replacement doses of testosterone to minimize the likelihood of falling into the concentration associated with tumor growth. We originally used testosterone 5 mg transdermal patches (Testoderm TTS, ALZA Pharmaceuticals, Palo Alto, CA, USA). This product was discontinued by the manufacturer, so we chose testosterone gel 1% CIII (AndroGel, Unimed Pharmaceuticals, Deerfield, IL, USA) for the remainder of the trial. If any grade 3 or 4 toxicity occurred during testosterone administration, the patient was evaluated to receive 150 mg of bicalutamide (Casodex, AstraZeneca, Wilmington, DE, USA) to counter the effects of testosterone. Tumor flare, defined as an increase in tumor-related symptoms during the first 2 wk of therapy, did not mandate withdrawal from the study unless it represented toxicity of grade ≥3.

The duration of testosterone repletion was escalated by cohort: Cohort 1 received 7 d of treatment, followed by a 4-wk observation period; cohort 2 received 4 wk of treatment, followed by a 4-wk observation period; and cohort 3 was treated until progression (Fig. 1). Cohorts 1 and 2 were designed to hold three to six patients; cohort 3 was intended to hold six patients by design.

2.3. Toxicity

National Cancer Institute Common Toxicity Criteria (NCI-CTC) v.2 were used. A history, physical exam, complete blood count (CBC), and chemistries were done prior to treatment, on days 2 and 4 and every week until study termination.

2.4. Serum drug levels

Serum levels of testosterone, free testosterone (FT), dihydrotestosterone (DHT), and sex-hormone–binding globulin (SHBG) were assayed on day 1, on day 4, and weekly thereafter. Patients applied the testosterone patch or gel on the night of day zero. Serum testosterone was determined by a competitive solid-phase radioimmunoassay (RIA; Coat-A-Count, Siemens Medical Solutions, Tarrytown, NY, USA). Assay imprecision at all concentrations levels was <10%. DHT was determined by a competitive solid-phase RIA. FT was determined by calculation after measuring SHBG, testosterone and albumin. The percent of FT is a function of the concentrations of SHBG, albumin, and testosterone, with the relative concentrations of testosterone and SHBG factoring in the dissociation constants for SHBG and albumin.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

2.5. Antitumor effects

Response assessments by PSA, bone scan, and soft-tissue imaging were performed every 8 wk and at study termination except in cohort 1, when repeat imaging was performed at week 5 (Fig. 1). WHO criteria were used for assessing changes in measurable disease. Posttreatment PSA alterations were recorded for all patients. Few assumptions were made regarding the clinical meaning of posttreatment PSA alterations because the treatment directly activates PSA expression. A sustained PSA increase of >50% from baseline over three tests was considered disease progression.

2.6. Correlative studies

Tissue biopsies from metastatic sites were obtained from consenting patients at baseline to determine the correlation between AR expression by immunohistochemistry with clinical outcomes. Primary antibodies (AR; Dako, Carpinteria, CA, USA) were applied to tissue sections at a dilution of 1:50 in 0.5% bovine serum albumin (BSA)/phosphate-buffered saline (PBS) and incubated overnight. The Dako LSAB2 detection system (catalog no. K0675) was used per the manufacturer's instructions, and the signal was developed with diaminobenzidine. Sections were counterstained in Mayer's hematoxylin followed by cover slipping. The cells were stained using immunohistochemistry, and the intensity of AR expression was measured (0, 1+, 2+, 3+).

Additionally, because PSA was felt to be an unreliable measure of treatment effect with this therapy, fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning, shown to be a useful indicator in previous prospective controlled clinical trials [14], was used to demonstrate treatment-related metabolic changes. FDG PET scans were obtained at baseline and at study termination for all cohorts. An FDG PET scan was also obtained during the week following treatment for cohorts 1 and 2 (weeks 2 and 5, respectively). PET scans were read via visual inspection and were categorized as progressing, stable, mildly responding, or responding.

2.7. Biostatistic considerations

The primary end point of the trial was to determine both the safety and the antitumor effects of exogenous high-dose testosterone. Dose-limiting toxicity was defined as grade ≥3 toxicity using NCI-CTC v.2. The maximum tolerated dose was defined as the highest dose level with an observed incidence of dose-limiting toxicity in two of six patients. If the risk of toxicity was 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, the probability of escalation was predicted to be 98%, 93%, 81%, 71%, 60%, 49%, 40%, 31%, 23%, or 17%, respectively.

3. Results

3.1. Patients

Twelve patients were treated. Table 1 contains demographics, disease status, and prior treatment histories. Eleven of the 12 patients had bone disease, and 3 out of 12 had measurable soft-tissue disease. By definition, all patients were castrate for at least 1 yr; the median number of hormonal manipulations was three. Five patients had progressed through prior taxane-based chemotherapy.

3.2. Treatment

Three patients were treated in both cohorts 1 and 2. Six patients in cohort 3 were treated until progression. All patients in cohorts 1 and 2 were treated with transdermal patches (six patients total), while all patients in cohort 3 were treated with testosterone gel. No patient changed the means of testosterone delivery midtreatment.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

3.3. Adverse events

Treatment was well tolerated in all cohorts, with no grade 3–4 episodes of pain. One patient in cohort 3 had a history of epidural disease prior to entering the study and developed low-grade back pain. He was found to have a T4 cord compression without any neurologic findings and experienced a 34% decline in PSA after 21 d on treatment. Follow-up computed tomography (CT) and bone scans after radiation to the spine revealed no new lesions.

Table 2 describes adverse events. Included in the table are all grade 3 or 4 events and any grade 1 or 2 event that affected a total of >25% of patients. Grade 1 and 2 fatigue affected all patients —a frequent finding for patients with castration-resistant disease. This was not felt to be the result of treatment, and anecdotally, some patients felt more energized on testosterone than off. Urinary frequency was also frequently seen (67% of patients). Although testosterone has the capacity to induce obstructive symptoms, no patient developed any grade of urinary retention or reported urinary frequency in excess of grade 2 (an increase of twice normal but less than hourly). Other low-grade events such as neuropathy, hyperglycemia, and anemia were likely not caused by treatment and were related to comorbid disease, preexisting conditions, and disease progression. Instances of grade 3 atrial fibrillation, cerebrovascular accident, hyperglycemia, and transaminitis were judged by the patients' treating physicians to be unrelated to treatment. There were no grade 4 adverse events.

3.4. Serum drug levels

Average levels of testosterone, FT, and DHT per patient are summarized in Table 3 and Figure 2. Cohort 1 had an average testosterone level of 560.5 ng/dl (range: 408.0–853.5) and DHT level of 61.8 ng/dl (range: 45.5–94). Cohort 2 had a higher average testosterone level of 737.2 ng/dl (range: 540.8–876.0) but a comparable DHT level of 63.2 ng/dl (37–105). Cohort 3 had a slightly lower testosterone level than cohort 1 (ie, 530.7 ng/dl [range: 342.5–768.6]) but the highest average DHT level (102.3 ng/dl [range: 79.9–104.4]). Note that all of these values except for the DHT level of cohort 3 are within physiologic range (normal range of DHT: 30–85 ng/dl).

3.5. Prostate-specific antigen levels

Posttreatment PSA nadirs for all patients are shown in the waterfall graph in Figure 3. A detailed description of every patient's PSA is found in Table 3. In cohort 1, PSA levels increased in all patients during the week of treatment. During the 1-mo observation period, PSA levels declined relative to the treatment period but did not return to baseline. In cohort 2, patients D and E demonstrated minor (<50%) PSA declines, while patient F's PSA rose. All patients demonstrated new lesions on bone scans. The only patient to recycle in cohort 2 was patient D. On day 5 of recycling, the patient presented with grade 2 tumor pain flare and grade 2 fever, and the patient's treating physician opted to stop therapy.

Representative PSA curves for patients in cohort 3 are shown in Figure 4. Patients G, J, K, and L demonstrated PSA declines of 26%, 50%, 34%, and 12%, respectively. Patients G, J, and L showed no progressive disease on standard scans. Patient K developed cord compression, as mentioned earlier, and received radiotherapy without neurologic sequelae. Patients H and I sustained PSA rises, with only H reaching the 50% mark. Both patients progressed radiographically.

3.6. Objective responses

Three patients had measurable soft tissue disease; no objective responses were seen. In total, 9 of 12 patients (75%) progressed either biochemically or radiographically, 1 (8%) patient demonstrated a PSA decline of 50% without radiographic progression, and 2 patients had

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

"stable" disease (PSA declines of 25% and 12% without radiographic progression). For cohort 3, median time on treatment was 84 d (range: 23–247).

3.7. Positron emission tomography scans

PET scans were performed to determine whether tumor glucose metabolism might fall despite a rising PSA. We saw no such phenomena. In 4 out of 11 patients with early posttreatment PET scans, PSA declined in the face of worsening PET results. In three patients, the PSA rose as PET scans worsened. Mixed associations were seen in the remaining four patients.

3.8. Pathology

A select number of patients elected to have posterior iliac crest bone marrow biopsies for determining tumor AR expression at baseline and shortly after treatment completion. Patients A, D, E, and H had both pre- and posttreatment biopsies. Patient A had pre- and posttreatment AR expression levels of 1+; patients D and E had pre- and posttreatment levels of 2–3+; patient H had a pretreatment level of 1+ and a posttreatment level of 3+. Patient J had a posttreatment biopsy only, revealing 3+ expression. There were too few specimens and too few responders to draw conclusions regarding the relationship between AR expression and clinical outcome or the success of preselecting the population for tumors with AR overexpression.

4. Discussion

The purpose of this trial was to determine whether exogenous high-dose testosterone was a safe strategy in patients with castration-resistant disease, despite a poor historical safety record. Indeed, our great fear was that we might recapitulate the history of flaring patients' cancers in the process of treating them with testosterone. We hypothesized that selecting patients on the basis of prolonged exposure to castration and treating them with high doses of testosterone would mirror the preclinical milieu that resulted in tumor growth repression and would optimize the likelihood of patient safety (if not benefit). Furthermore, we hypothesized that the use of contemporary safety monitoring would allow a sufficient level of surveillance and early detection of disease progression to minimize patient risk.

Congruent with our hypothesis and expectations, no patient developed an early tumor flare (defined as grade 3 pain) or a new need for opiates or required intervention with high-dose bicalutamide. One patient with an existing spinal bone lesion, however, did develop cord compression after 3 wk on study. The fact that he had preexisting epidural disease strongly suggests that men should undergo a screening magnetic resonance imaging scan of the spine to rule out high-risk lesions prior to initiating treatment. Save for this patient with a presumably preventable problem, patients tolerated therapy well, suggesting that phase 2 investigations of this approach, treating patients to progression, can be performed safely. These data are supported by two other recent clinical trials of patients with metastatic PCa in which exogenous testosterone was administered safely as part of hormonal and chemohormonal therapy in men whose cancer was not castration resistant [15,16].

This trial was only designed to establish preliminary safety data, not efficacy; in fact, cohorts 1 and 2 used such a brief treatment period that treatment effects are not interpretable. Furthermore, too few patients were involved in this study to reach any efficacy-based conclusions. One patient did achieve a PSA decline of 50% without a demonstrable increase in radiographic metastases on standard imaging studies. Although this "responder" may suggest that this study identified patients who mirror the growth repression seen preclinically, this patient was exceptional; however, other patients enjoyed lesser PSA declines. No patients with measurable disease could be characterized as having achieved a partial or complete response.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Given that this approach has proved to be safe, especially if patients are screened for high-risk spinal lesions, several issues are raised relating to future studies. The first regards eligibility. Although all of these patients met the definition of castration-resistant metastatic disease, they likely still represented a biologically heterogeneous group. They had various exposures to prior hormonal therapies and chemotherapy and likely also had variable AR expression. Regarding the latter, when the present study was designed, there were few means by which patients might be selected on the basis of AR overexpression, which, as previously mentioned, predicts for response preclinically. Now, however, such methods exist. Patients with AR-rich tumors, for example, can be identified using fluorinated dihydrotestosterone (FDHT) PET tracers [17, 18]. Additionally, circulating PCa cells can be isolated and identified on the basis of AR gene amplification [19]. These techniques as well as further efforts to reduce patient heterogeneity can be used to enrich the patient population for likely responders in future trials. Patient selection is of particular importance in this approach because although testosterone may be beneficial to some patients, it may activate cancer growth in others, representing a deleterious rather than a beneficial effect.

The second modification would be response criteria. PSA Working Group II Consensus Criteria [20] had not been developed when this trial was designed. Posttreatment PSA alterations were generally poorly informative in this study. We anticipated that PSA might rise despite antitumor responses, but patients whose PSA levels rose also progressed radiographically by standard imaging modalities, with no major response seen by PET scanning. PSA declines were also not necessarily indicative of a favorable outcome, as four of six patients in cohorts 2 and 3 whose PSA levels declined also demonstrated disease progression clinically or on scans. For the next trial, we intend to follow PSA Working Group II Consensus Criteria and only use radiographic or clinical progression as an end point, using two new lesions on two successive bone scans as the definition for progression in bone [20].

The final consideration is that of dose. Despite using three times the usual replacement dose of testosterone, serum testosterone levels did not, on average, exceed normal levels. These levels may be a result of inefficient absorption but could also result from metabolism to DHT and other downstream products. Cohort 3 did have supraphysiologic DHT levels. It is not clear from preclinical data whether growth inhibition arises from testosterone or DHT or both, but if indeed supraphysiologic testosterone levels are necessary to repress growth, then it is possible that such levels cannot be achieved without also administering a 5α-reductase inhibitor (5-ARI) [21]. We are exploring this hypothesis in an upcoming clinical trial.

5. Conclusions

In conclusion, this study shows that high-dose exogenous testosterone can be administered safely to patients with castration-resistant disease. We plan to explore this concept further in a study that enriches the castration-resistant population for AR overexpression using FDHT scans and circulating cells, that utilizes PSA Working Group II response criteria, and that explores maximizing testosterone levels by the addition of a 5-ARI.

Acknowledgments

Funding/Support and role of the sponsor: Prostate Cancer Foundation, PepsiCo, Sacerdote Fund, NIH CA102544 and K23102544

References

1. Huggins C, Hodges CV. Studies on prostatic cancer, effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941;1:293–7.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

2. Huggins C, Stevens RE Jr, Hodges CV. Studies on prostatic cancer. II. The effect of castration on advanced carcinoma of the prostate gland. Arch Surg 1941;43:209–23.
3. Kokontis J, Takakura K, Hay N, Liao S. Increased androgen receptor activity and altered c-myc expression in prostate cancer cells after long-term androgen deprivation. Cancer Res 1994;54:1566–73. [PubMed: 7511045]
4. Kokontis JM, Hay N, Liao S. Progression of LNCaP prostate tumor cells during androgen deprivation: hormone-independent growth, repression of proliferation by androgen, and role for p27kip1 in androgen-induced cell cycle arrest. Mol Endocrinol 1998;12:941–53. [PubMed: 9658399]
5. Koivisto P, Kononen J, Palmberg C, et al. Androgen receptor gene amplification: a possible molecular mechanism for androgen deprivation failure in prostate cancer. Cancer Res 1997;57:314–9. [PubMed: 9000575]
6. Koivisto P, Visakorpi T, Kallioniemi OP. Androgen receptor gene amplification: a novel molecular mechanism for endocrine therapy resistance in human prostate cancer. Scand J Clin Lab Invest 1996;226(suppl):57–63.
7. Umekita Y, Hiipakka RA, Kokontis JM, Liao S. Human prostate tumor growth in athymic mice: inhibition by androgens and stimulation by finasteride. Proc Natl Acad Sci U S A 1996;93:11802–7. [PubMed: 8876218]
8. Joly-Pharaboz MO, Soave MO, Nicolas B, et al. Androgens inhibit the proliferation of a variant of the human prostate cancer cell line LNCaP. J Steroid Biochem Mol Biol 1995;55:67–76. [PubMed: 7577722]
9. Fowler JE Jr, Whitmore WF Jr. The response of metastatic adenocarcinoma of the prostate to exogenous testosterone. J Urol 1981;126:372–5. [PubMed: 7277602]
10. Manni A, Bartholomew M, Caplan R, et al. Androgen priming and chemotherapy in advanced prostate cancer: evaluation of determinants of clinical outcome. J Clin Oncol 1988;6:1456–66. [PubMed: 3047336]
11. Suarez AJ, Lamm DL, Radwin HM, Sarosdy M, Clark G, Osborne CK. Androgen priming and cytotoxic chemotherapy in advanced prostatic cancer. Cancer Chemother Pharmacol 1982;8:261–5. [PubMed: 7127658]
12. Pearson OH. Discussion of Dr. Huggins' paper: control of cancers of man by endocrinological methods. Cancer Res 1957;17:473–9. [PubMed: 13437312]
13. WHO Offset Publication No. 48. Geneva, Switzerland: World Health Organization; 1979. WHO Handbook for Reporting Results of Cancer Treatment.
14. Morris MJ, Akhurst T, Larson SM, et al. Fluorodeoxyglucose positron emission tomography as an outcome measure for castrate metastatic prostate cancer treated with antimicrotubule chemotherapy. Clin Cancer Res 2005;11:3210–6. [PubMed: 15867215]
15. Rathkopf D, Carducci MA, Morris MJ, et al. Phase II trial of docetaxel with rapid androgen cycling for progressive noncastrate prostate cancer. J Clin Oncol 2008;26:2959–65. [PubMed: 18565882]
16. Feltquate D, Nordquist L, Eicher C, et al. Rapid androgen cycling as treatment for patients with prostate cancer. Clin Cancer Res 2006;12:7414–21. [PubMed: 17189414]
17. Zanzonico PB, Finn R, Pentlow KS, et al. PET-based radiation dosimetry in man of 18F-fluorodihydrotestosterone, a new radiotracer for imaging prostate cancer. J Nucl Med 2004;45:1966–71. [PubMed: 15534070]
18. Larson SM, Morris M, Gunther I, et al. Tumor localization of 16beta-18F-fluoro-5alpha-dihydrotestosterone versus 18F-FDG in patients with progressive, metastatic prostate cancer. J Nucl Med 2004;45:366–73. [PubMed: 15001675]
19. Shaffer DR, Leversha MA, Danila DC, et al. Circulating tumor cell analysis in patients with progressive castration-resistant prostate cancer. Clin Cancer Res 2007;13:2023–9. [PubMed: 17404082]
20. Scher HI, Halabi S, Tannock I, et al. 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. J Clin Oncol 2008;26:1148–59. [PubMed: 18309951]
21. Eggener SE, Stern JA, Jain PM, et al. Enhancement of intermittent androgen ablation by “off-cycle” maintenance with finasteride in LNCaP prostate cancer xenograft model. Prostate 2006;66:495–502. [PubMed: 16372330]

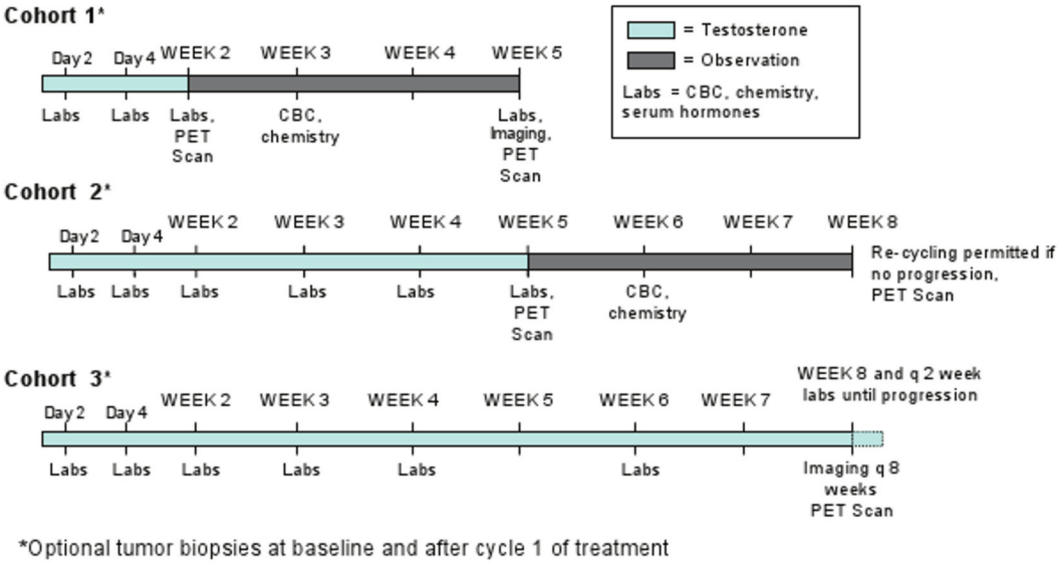

Fig. 1. Treatment schema

CBC = complete blood count; PET = positron emission tomography.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

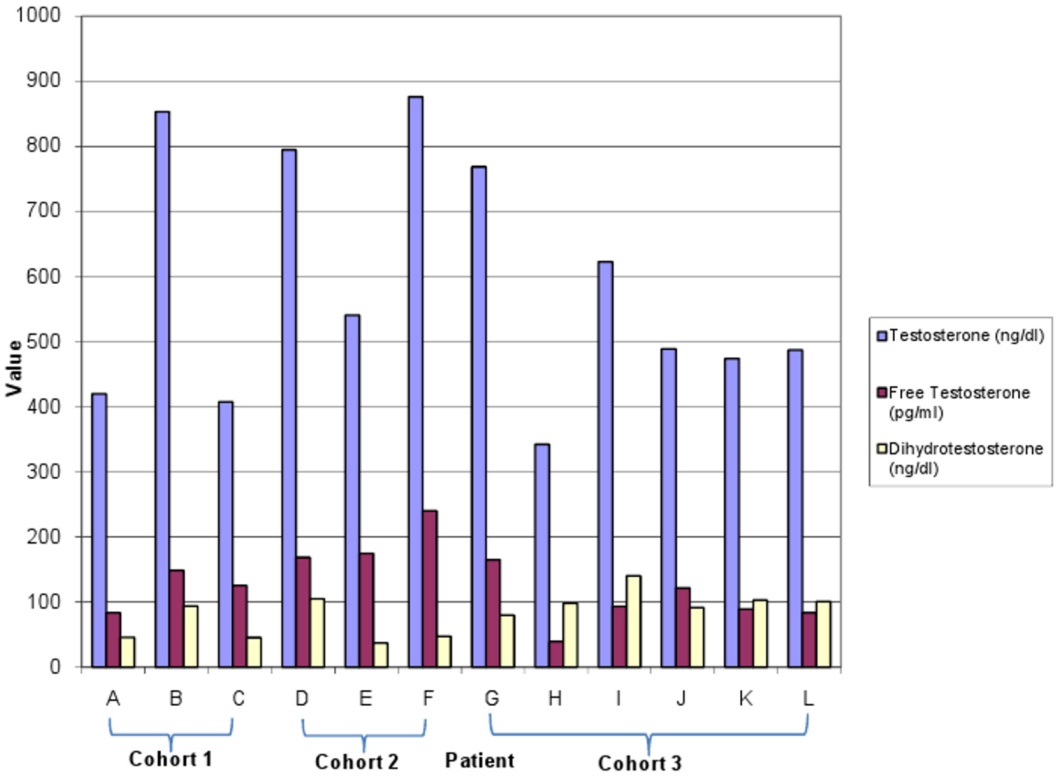

Fig. 2. Serum androgen levels: Reference ranges for these assays were 181–758 ng/dl for testosterone, 47–244 pg/ml for free testosterone, and 30–85 ng/dl for dihydrotestosterone

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

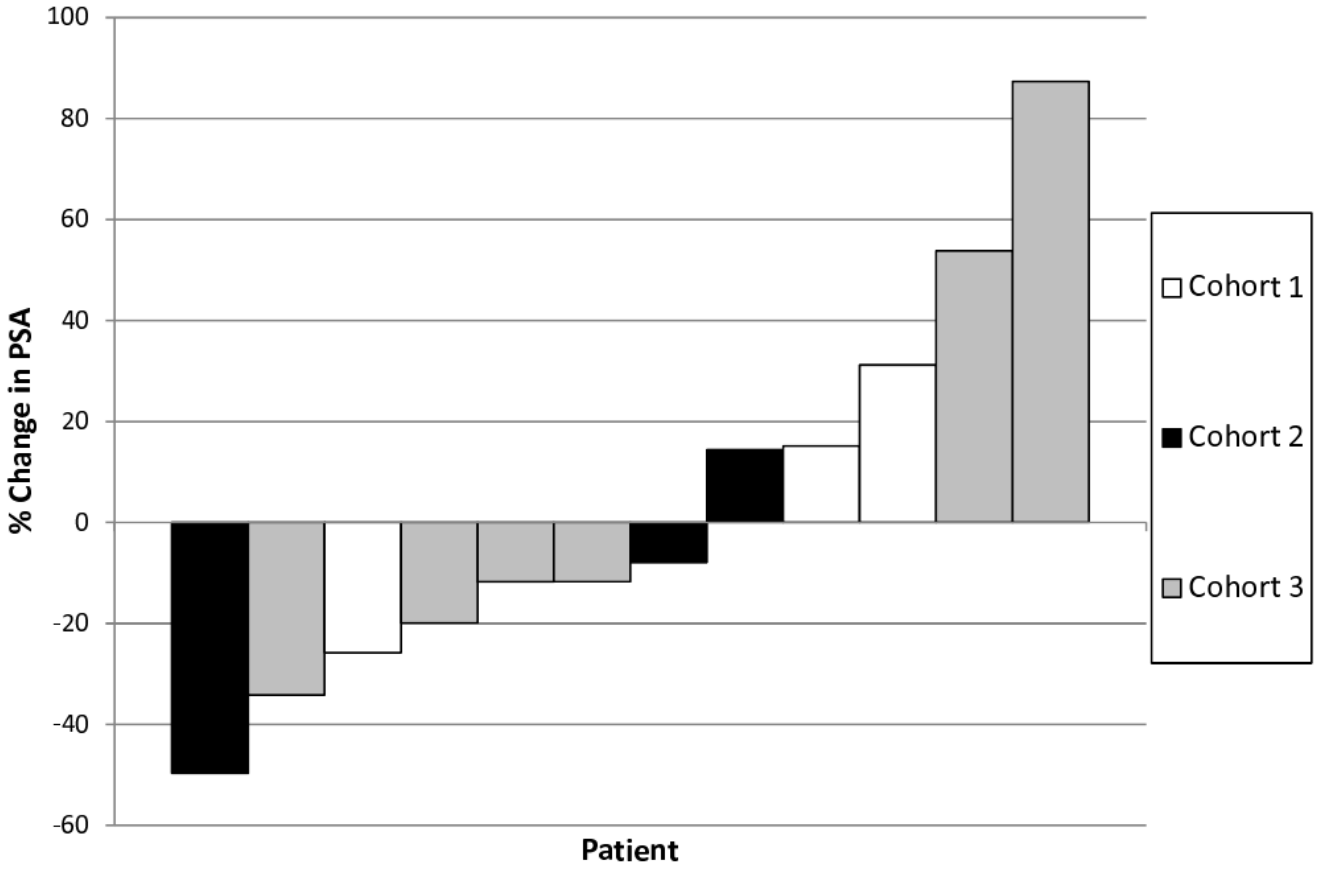

Fig. 3. Percent change in prostate-specific antigen achieved by all patients while on study
PSA = prostate-specific antigen.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

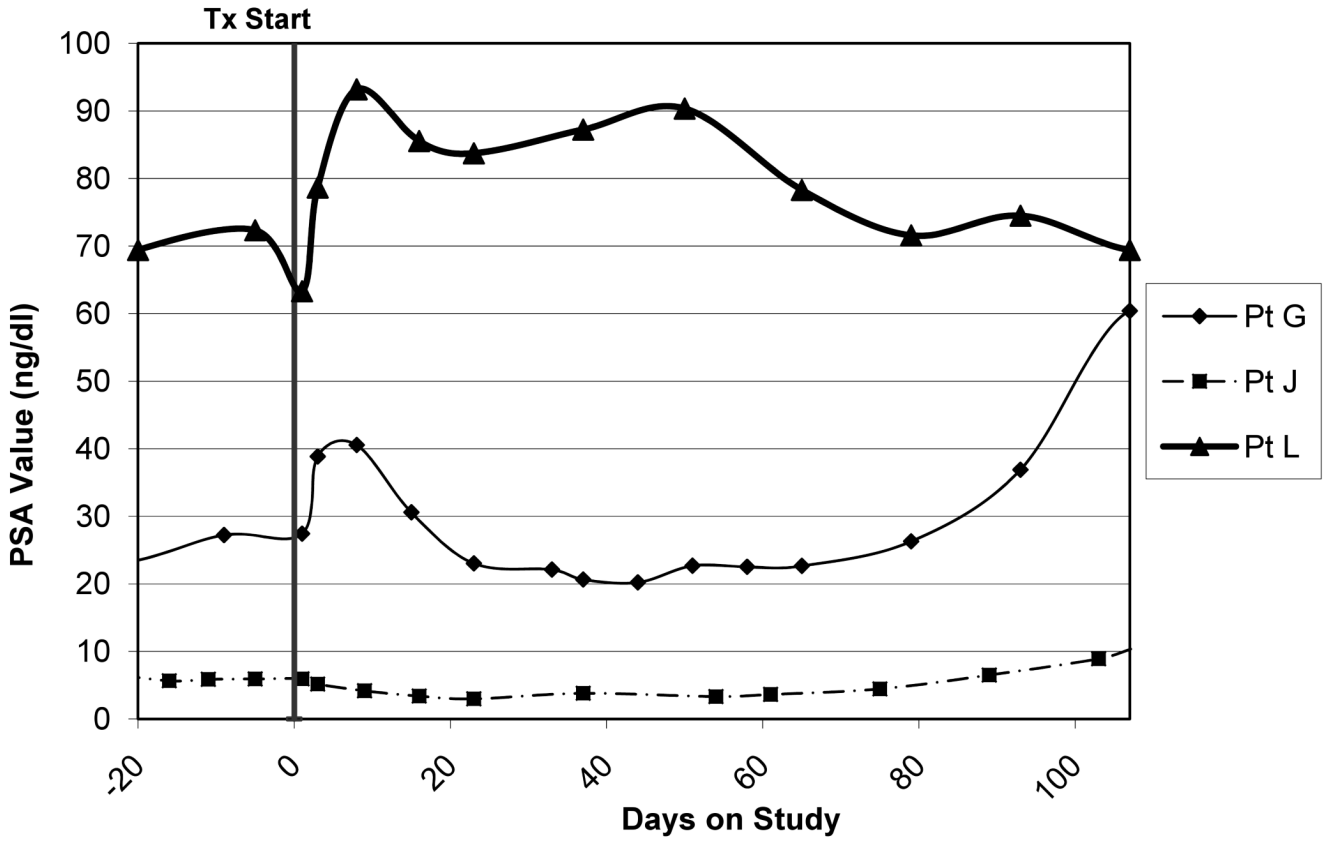

Fig. 4. Prostate-specific antigen kinetics of representative patients treated to progression as part of cohort 3 (truncated at 109 d of treatment to enhance readability)

PSA = prostate-specific antigen; Pt = patient.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 1

Patient characteristics (n = 12)

Characteristics	No. of patients
Bone disease only	9
Soft tissue disease only	1
Bone and soft tissue	2
Median age, yr (range)	65 (46–77)
Median Karnofsky PS (range)	90 (80–90)
Median Gleason grade (range)	8 (7–9)
Median PSA (range)	91 (6–2637)
Median no. of prior hormonal regimens (range)	3 (2–5)
One prior regimen	0
Two prior regimens	2
Three prior regimens	8
Four prior regimens	1
Five prior regimens	1
Prior RT	6/12
Primary (prostate)	2/6
Palliative (other sites)	4/6
Prior surgery (prostatectomy)	5/12
Prior chemotherapy	5/12
One prior regimen	0
Two prior regimens	0
Three prior regimens	3
Four prior regimens	2

PS = performance status; PSA = prostate-specific antigen; RT = radiotherapy.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 2

Adverse events

Events*		**Grade, *n* (%)**			
		1+	**2+**	**3+**	**4+**
Cardiac	Atrial fibrillation	0 (0)	0 (0)	1 (8)	0 (0)
Neurologic	CVA	0 (0)	0 (0)	1 (8)	0 (0)
	Cord compression	0 (0)	0 (0)	1 (8)	0 (0)
	Neuropathy	6 (50)	1 (8)	0 (0)	0 (0)
Hematologic	Anemia	6 (50)	2 (17)	0 (0)	0 (0)
	Leukopenia	1 (8)	1 (8)	0 (0)	0 (0)
Metabolic	Hyperglycemia	6 (50)	1 (8)	1 (8)	0 (0)
Gastrointestinal	Liver toxicity (SGOT)	5 (42)	0 (0)	1 (8)	0 (0)
	Liver toxicity (SGPT)	2 (17)	2 (17)	1 (8)	0 (0)
	Nausea	2 (17)	2 (17)	0 (0)	0 (0)
General	Tumor pain	5 (42)	4 (33)	0 (0)	0 (0)
	Fatigue	9 (75)	3 (25)	0 (0)	0 (0)
	Edema	1 (8)	1 (8)	0 (0)	0 (0)
	Hematuria	0 (0)	3 (25)	0 (0)	0 (0)
	Urinary frequency	6 (50)	2 (17)	0 (0)	0 (0)

CVA = cerebrovascular accident; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

* Grade 1 and 2 toxicities were reported only for effects observed at a frequency ≥25%.

All grade 3 and 4 events are reported.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 3

Summary of prostate-specific antigen responses and antitumor activity

Patient	Cohort	Days on study	No. of cycles	Average testosterone level on Tx[a], ng/dl	Average FT level on Tx[a], pg/ml	Average DHT level on Tx[a], ng/dl	Pre-Tx PSA, ng/dl	Best PSA response, ng/dl	Change in PSA, %	Soft tissue change	Bone scan	Initial follow-up FDG PET scan	Off-study FDG PET scan
A	1	65	1	420	83.5	46.0	2271	2615.36	5.16b	N/A	No new lesions	PD	SD
B	1	46	1	853.5	148.6	94.0	378.66	496.85	31.21[b]	N/A	No new lesions	SD	SD
C	1	121	1	408.0	125.2	45.5	147.52	118.21	−19.87[b]	N/A	New lesions	PD	SD
D	2	57	2	794.8	168.6	105.0	41.12	37.87	−7.9	N/A	New lesions	SD	SD
E	2	52	1	540.8	174.6	37.0	143.88	127.03	−11.71[b]	N/A	New lesions	PD	PD
F	2	57	1	876.0	240.2	47.6	20.63	31.73	53.81[b]	N/A	New lesions	PD	MILD IMP
G	3	109	2	768.6	165.2	79.9	27.22	20.2	−25.79	N/A	No new lesions	PD	MILD IMP
H	3	60	1	342.5	39.4	98.0	64.16	120.2	87.34	POD (54% increase)	New lesions	Mild improve ment	N/A
I	3	61	1	622.7	93.5	140.4	108.41	124	14.38	POD ↑ 79%	New lesions	PD	N/A
J	3	124	2	489.1	121.8	91.6	5.92	2.98	−49.66	N/A	No new lesions	PD	N/A
K	3	27	1	474.0	89.7	103.0	217.42	143.13	−34.17	N/A[c]	No new lesions[c]	N/A	N/A
L	3	250	4	487.4	84.0	101.0	72.33	63.82	−11.77	SD (24%decrease)	N/A	Mild improve ment	N/A

CT = computed tomography; DHT = dihydrotestosterone; FDG = fluorodeoxyglucose; FT = free testosterone; N/A = not applicable; PD = progressive disease; PET = positron emission tomography; POD = peroxidase; RT = radiotherapy; SD = stable disease; Tx = therapy.

[a] Reference values: testosterone 181–758 ng/dl, FT 47–244 pg/ml, DHT 30–85 ng/dl.

[b] During observation.

[c] Only available follow-up CT and bone scan occurred after patient had RT to spine for cord compression.