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Phase II Study of Dutasteride for Recurrent Prostate Cancer During Androgen Deprivation Therapy

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Abstract

Purpose—We determined the response rate to and safety of a dual 5α-reductase inhibitor, dutasteride, in men with castration recurrent prostate cancer.

Materials and Methods—A total of 28 men with asymptomatic castration recurrent prostate cancer were treated with 3.5 mg dutasteride daily (luteinizing hormone-releasing hormone treatment continued), and evaluated monthly for response and toxicity. Eligibility included appropriate duration antiandrogen withdrawal, baseline prostate specific antigen 2.0 ng/ml or greater and a new lesion on bone scan, increase in measurable disease using Response Evaluation Criteria in Solid Tumors criteria, or 2 or more consecutive prostate specific antigen measurements increased over baseline. Outcomes were progression, stable disease, partial response (prostate specific antigen less than 50% of enrollment for 4 or more weeks) or complete response.

Results—There were 25 evaluable men with a mean age of 70 years (range 57 to 88), a mean prostate specific antigen of 61.9 ng/ml (range 5.0 to 488.9) and mean Gleason score 8 (range 6 to 10), 15 of whom had bone metastases. Eight men had 10 grade 3 or higher adverse events using National Cancer Institute Common Terminology Criteria, all of which were judged to be unrelated to treatment. Of the 25 men 14 had disease progression by 2 months, 9 had stable (2.5, 3, 3, 4, 4, 5, 5, 8.5, 9 months) disease, 2 had a partial response and none had a complete response. Overall median time to progression was 1.87 months (range 1 to 10, 95% CI 1.15–3.91).

Conclusions—Dutasteride rarely produces biochemical responses in men with castration recurrent prostate cancer. However, further study is warranted given its favorable safety profile.

Keywords

dutasteride; prostatic neoplasms; clinical trial; phase II; prostate

Prostate cancer is the most common noncutaneous malignancy of American men. The initial treatment for those in whom local therapy fails or metastasis develops is androgen deprivation therapy. Invariably prostate cancer recurs and treatment options are limited.

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Castration recurrent prostate cancer is often referred to as androgen independent or hormone refractory. However, high levels of expression of the androgen receptor and androgen receptor regulated genes suggest a continued role for the androgen receptor in prostate cancer recurrence.[1] Dihydrotestosterone, the preferred androgen receptor ligand, is produced from testosterone in androgen stimulated benign prostatic tissue, predominantly by the enzyme 5α-reductase type II. However, in castration recurrent prostate cancer the 5α-reducing capacity switches toward type I isozyme.[2] Furthermore, castration recurrent prostate cancer tissue has DHT levels sufficient for androgen receptor transactivation whether measured using radioimmunoassay or mass spectrometry.[2,3] These findings suggest that dutasteride, which inhibits both isozymes of 5αR, may be useful in castration recurrent prostate cancer. Finasteride, which primarily inhibits the type II isozyme, infrequently produces remission in castration recurrent prostate cancer.[4]

Dutasteride is well tolerated and safe in men with lower urinary tract symptoms but its safety in men with castration recurrent prostate cancer remains unclear.[5] In this study we determined the safety of and response rate to dutasteride in men with castration recurrent prostate cancer.

MATERIALS AND METHODS

A total of 28 men with asymptomatic prostate cancer progression despite medical (LHRH agonist with or without antiandrogen) or surgical castration were enrolled in an institutional review board approved phase II study. The Prostate Specific Antigen Working Group definition of progressive disease was used for eligibility, that is 1) increased size of measurable lesions on radiographic study using RECIST, 2) new lesion on bone scan, or 3) 2 successive increases in PSA measured at least 1 week apart.[6,7] No minimum increase in PSA was required. Other eligibility criteria included serum PSA 2.0 ng/ml or greater, appropriate duration of antiandrogen cessation (28 days or greater for flutamide, 42 days or greater for biclutamide or nilutamide), and Eastern Cooperative Oncology Group performance status 2 or less. PSA doubling time was calculated using 3 or more values.

Dutasteride was administered daily at 3.5 mg until intolerable toxicity or evidence of disease progression. All patients were monitored with physical examinations and laboratory studies which included serum PSA at the initiation of therapy and every 4 weeks thereafter. Toxicity was graded using the NCI Common Toxicity Criteria.

After entry into the study disease progression was defined by any of 4 criteria, namely 1) appearance of new lesions suspicious for metastatic disease on bone scan, 2) increase in radiographically measurable disease using RECIST, 3) greater than 25% increase in serum PSA compared to baseline or posttreatment nadir, whichever was lower, and increase 5.0 ng/ml or greater, or 4) development of symptoms directly related to prostate cancer.

Complete response to treatment required disappearance of all clinical evidence of disease and normalization of PSA (less than 0.2 ng/ml on 2 successive determinations). Partial response was a greater than 50% decrease in serum PSA that persisted 4 or more weeks, or a 30% or greater decrease in the sum of the longest diameter of all metastatic target lesions using RECIST. Disease was considered stable if it did not meet the criteria for progression, or partial or complete response.

An exact 1-stage design was used to evaluate efficacy. Since the median TTP after cytotoxic chemotherapy (docetaxel) in this setting was 10 months, the primary efficacy analysis based on this historical control involved a 2-sided test of the null hypothesis that the 10-month probability of progression was 50%.[8] The alternative was that the rate was less than or greater than 50%. A 1-sample binomial test was used to determine if the rate of patients without treatment failure at 10 months was different from 50%. The upper bound on the type I error

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was set to be 0.05. Sample size was determined such that the lower bound of the statistical power for correctly concluding a difference in TTP exists was 0.80 if the true 10-month progression rate was 80% or greater, or 23% or less. The overall survival and estimated progression-free survival distribution were obtained using the Kaplan-Meier method. Statistical analysis was performed using SAS® 9.1.3.

RESULTS

A total of 28 patients were enrolled in the study between February 2005 and February 2007 at Roswell Park Cancer Institute (23) and Louisiana State University Health Sciences Center (5). Two patients were lost to followup due to Hurricane Katrina and 1 declined participation after enrollment. Mean age of the 25 evaluable subjects was 70 years (range 57 to 88), mean Gleason score was 8 (range 6 to 10) and 15 had bone metastases. Fourteen (56%) patients met the eligibility criteria for progressive disease because of PSA progression only, and 11 (44%) met the criteria of PSA progression and new lesions on bone scan. No patient met eligibility criteria because of RECIST. At entry mean baseline PSA was 61.9 ng/ml (range 5.0 to 488.9). Mean and median pre-entry PSA doubling times were 8 and 4 months, respectively, with a range of −4 to 68.

Nine (36%) patients had undergone prior single modality local therapy (radical prostatectomy or radiotherapy), and 7 (28%) had undergone radical prostatectomy and salvage radiotherapy. The remaining 9 (36%) patients had been treated only with androgen deprivation therapy. Prior systemic treatments consisted of only LHRH agonists for 1 (4%) patient, LHRH agonists and antiandrogens for 19 (76%), and orchiectomy and antiandrogens for 2 (8%). The remaining 3 patients (12%) were treated with LHRH agonists and antiandrogens plus ketoconazole and prednisone (1 patient), dexamethasone and intravenous calcitriol (1 patient), and dexamethasone, fulvestran and intravenous calcitriol (1 patient).

Eight men experienced 10 grade 3 or higher adverse events using NCI criteria. All of these events (hypokalemia, hyperglycemia, gross hematuria, anemia, urine retention, deep venous thrombosis, stroke, ileus and acute renal insufficiency) were judged to be unrelated to treatment (see table).

Median TTP was 1.87 months (range 1 to 10, 95% CI 1.15–3.91) (fig. 1). Fourteen patients (56%) had disease progression within 2 months, 9 (36%) had stable disease for a mean of 5 months (range 3 to 9) (fig. 2) and 2 (8%) had a partial response for a mean of 8 months (range 6 to 11). The 95% CI based on the binomial distribution for the partial response rate was 0.001 to 0.204. No patient had a complete response. The 10-month progression rate was 96%. There was a significant difference in median time to progression compared to docetaxel ($p < 0.05$). At a median followup of 25 months 8 of 14 patients with progression had died (57%), 2 of 9 patients with stable disease had died (22%) and no patients with partial response had died (fig. 3). The 25th percentile for overall survival was 16.6 months. Mean pre-entry PSA doubling times were 3 months for patients with progressive disease (range −4 to 6), 11 months for those with stable disease (range 1 to 68) and 26 months for those with a partial response (range 9 to 43).

A 66-year-old man with Gleason grade 5 + 4 = 9, pT2bN0M0 prostate cancer, who had received LHRH agonist for biochemical recurrence after radical prostatectomy and salvage radiotherapy, had a partial response and did not have progression for 11 months (fig. 4). A 69-year-old man with Gleason grade 4 + 3 = 7, cT2NxM1 prostate cancer, who had only been treated previously with systemic therapy (LHRH agonist, antiandrogen, dexamethasone and intravenous calcitriol), had a partial response and did not have progression for 5 months (fig. 5).

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DISCUSSION

Until the last decade most clinicians believed that cytotoxic chemotherapy had no role in the management of castration recurrent prostate cancer.[9] Since then mitoxantrone and docetaxel have shown some benefit in this setting.[10] Docetaxel produced a median survival advantage of approximately 2 months, and was granted Food and Drug Administration approval for castration recurrent prostate cancer. Unfortunately cytotoxic chemotherapy has important side effects. Men with castration recurrent prostate cancer who are asymptomatic are less likely to accept such toxic therapies especially when cancer recurrence is manifested only biochemically. The identification of less toxic therapies for such men would have obvious benefits.

The current study revealed no toxicities that were considered related to dutasteride. Men with castration recurrent prostate cancer experienced the well documented safety profile of this drug. The grade III toxicities that were observed were likely related to underlying disease processes or medical comorbidities. Dutasteride has been administered at doses up to 40 mg per day for 7 days without significant adverse effects, and at doses of 5 mg daily for 6 months with a safety profile similar to the 0.5 mg dose used clinically.[11,12] In the current study a dose of 3.5 mg was chosen to maximize efficacy while maintaining ease of administration since 3.5 mg capsules were available.

No complete responses to dutasteride were found using the criteria adopted a priori. Overall the partial response rate was 8%. Response rates this low are usually considered of no interest. Five men with stable disease showed no evidence of PSA decrease and had PSA doubling times sufficiently long that stable disease criteria were met because of the time required for PSA to increase 25% and 5 ng/ml or more as per the arbitrary progression criteria. However, 4 men with stable disease appeared to have some biochemical response to dutasteride (fig. 2). Larger studies would help clarify what percentage of men with stable disease has a clinically meaningful reduction in PSA increase.

Currently available secondary hormonal therapies have modest response rates but more significant side effects. Ketoconazole demonstrated a partial response rate of 27% in patients with castration recurrent prostate cancer. However, 21% of patients experienced grade 3 or 4 treatment related side effects. 13 Corticosteroids demonstrated a partial response in 20% to 30% of patients with a median response duration of 4 months.[14] Steroids are well-known to cause poor wound healing, skin changes, and alterations in body fat, fluid retention, weight gain and hypertension. In another study diethylstilbestrol, a synthetic estrogen, had a 21% response rate in castration recurrent prostate cancer. Diethylstilbestrol related toxicities include thromboembolic events (myocardial infarction, stroke or pulmonary embolism) and gynecomastia.[15] In comparison to these agents dutasteride demonstrated a lower response rate, but in light of its more favorable side effect profile dutasteride may still be a potentially better initial choice among secondary hormonal agents for those patients with asymptomatic castration recurrent prostate cancer.

LY320236, another dual 5αR inhibitor, also demonstrated activity in castration recurrent prostate cancer. In a phase II study of 51 men with advanced prostate cancer 4 of 15 (27%) men with castration recurrent prostate cancer had a greater than 50% decrease in serum PSA that persisted 56 to 1,000+ weeks.[16] LY320236 was well tolerated in the study with only 3 of 51 patients experiencing reversible NCI grade 3–4 toxicity (diarrhea, elevated liver enzymes), although drug development was later discontinued due to its teratogenicity. However, using the same response criteria only 2 of 25 men (8%) responded to dutasteride in the current study. Most men in both studies did not experience a biochemical or radiographic response.

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The reason for the limited response to dual 5αR inhibitors in castration recurrent prostate cancer is unclear. The expression of androgen receptor regulated growth genes may continue because of accumulation of testosterone, which activates the androgen receptor, but not as well as DHT or aromatization of testosterone to estrogen, which may activate mutant androgen receptors.[17–20] In the LY320236 study the serum estradiol level was below the limit of detection before treatment but increased to 17.8 and 30.0 pg/ml after the 250 and 500 mg doses, respectively. Testosterone and DHT levels did not change appreciably with treatment. Therefore, inhibition of 5αR activity may increase formation of estradiol by favoring aromatization of androgens in lieu of reduction.

The current study had several limitations. As a phase II study the number of patients recruited was small. A larger trial is needed to test the ability of dutasteride to induce biochemical and radiographic response in patients with castration recurrent prostate cancer. In addition, patients in this study received a variable number, and nonstandardized dose and duration of prior cancer treatments including radiation therapy, radical prostatectomy and systemic therapy. What effect these treatments had on the response to dutasteride was unclear. The duration of prior systemic treatments was also not known for all patients. The frequency of PSA tests (every 4 weeks) could have increased the chance of laboratory error since frequent measurement may capture individual biological variation and not biochemical progression. Lastly, the true response rate to dutasteride may have been influenced by the arbitrary definition of stable disease. Of the 9 men with stable disease 5 had baseline PSA doubling times such that PSA may not have increased by 25% and 5 ng/ml even without treatment. They may have been labeled as having stable disease although dutasteride truly had no effect. Furthermore, since 5αR inhibition amounts to hormonal manipulation of androgens and PSA is influenced by androgens, the meaning of decreased PSA in patients with stable disease is unclear.

CONCLUSIONS

Dutasteride rarely produces biochemical responses in men with castration recurrent prostate cancer. However, further study is warranted given its favorable safety profile.

Abbreviations and Acronyms

5αR	5α-reductase
DHT	dihydrotestosterone
LHRH	luteinizing hormone-releasing hormone
NCI	National Cancer Institute
PSA	prostate specific antigen
RECIST	Response Evaluation Criteria in Solid Tumors
TTP	time to progression

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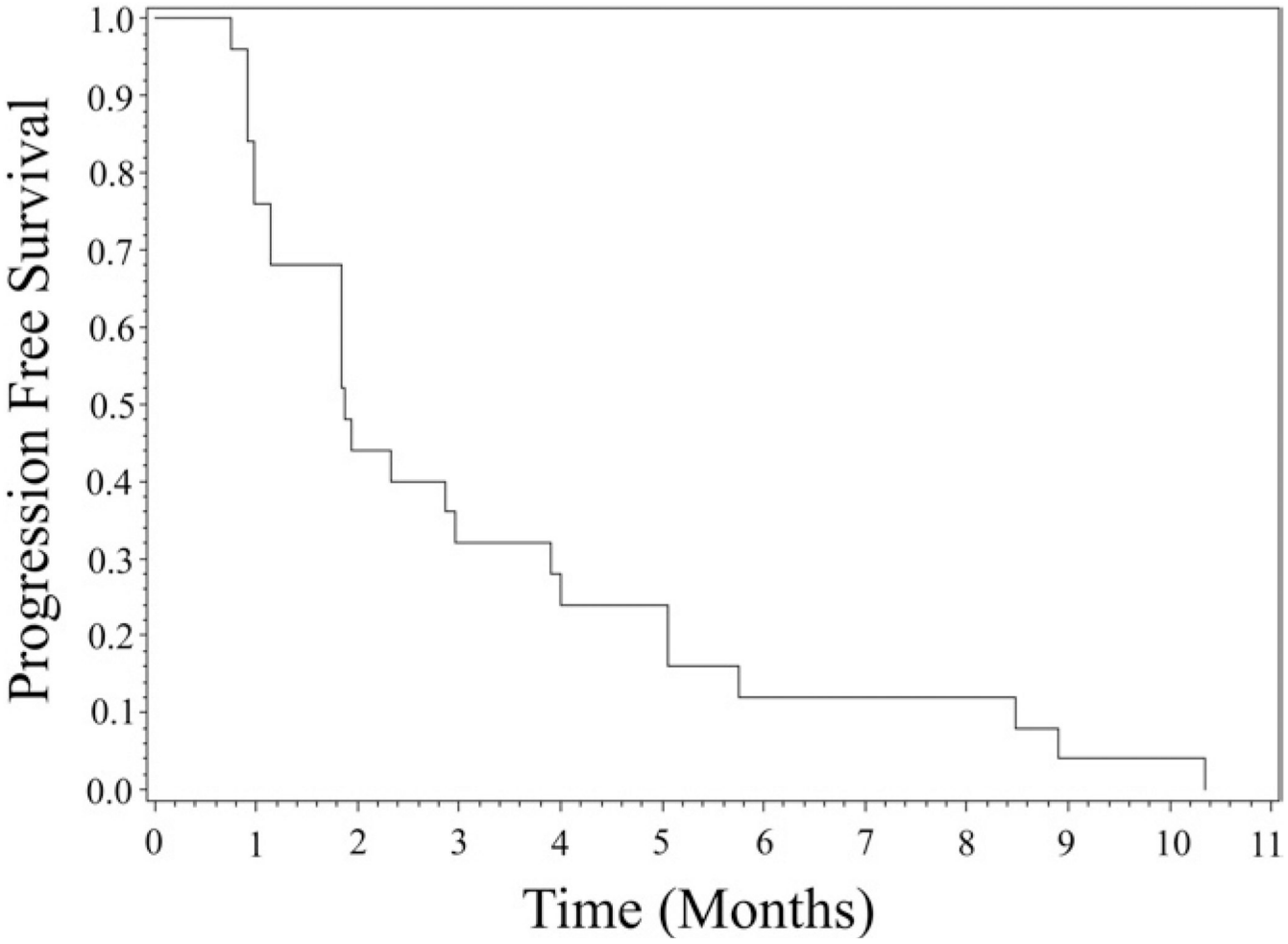

Figure 1.
Kaplan-Meier time to disease progression

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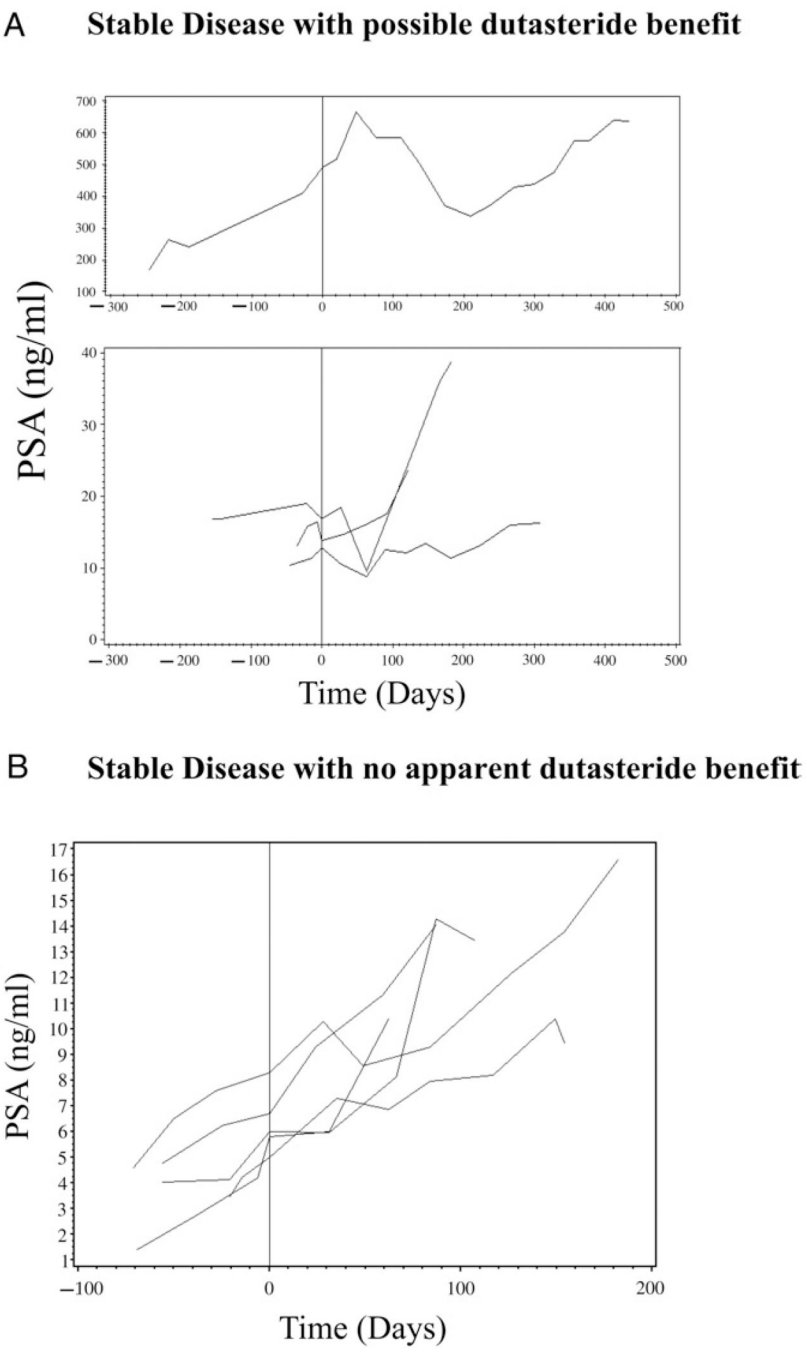

Figure 2.
PSA response among patients with stable disease. *A*, stable disease with possible dutasteride benefit. *B*, stable disease with no apparent dutasteride benefit.

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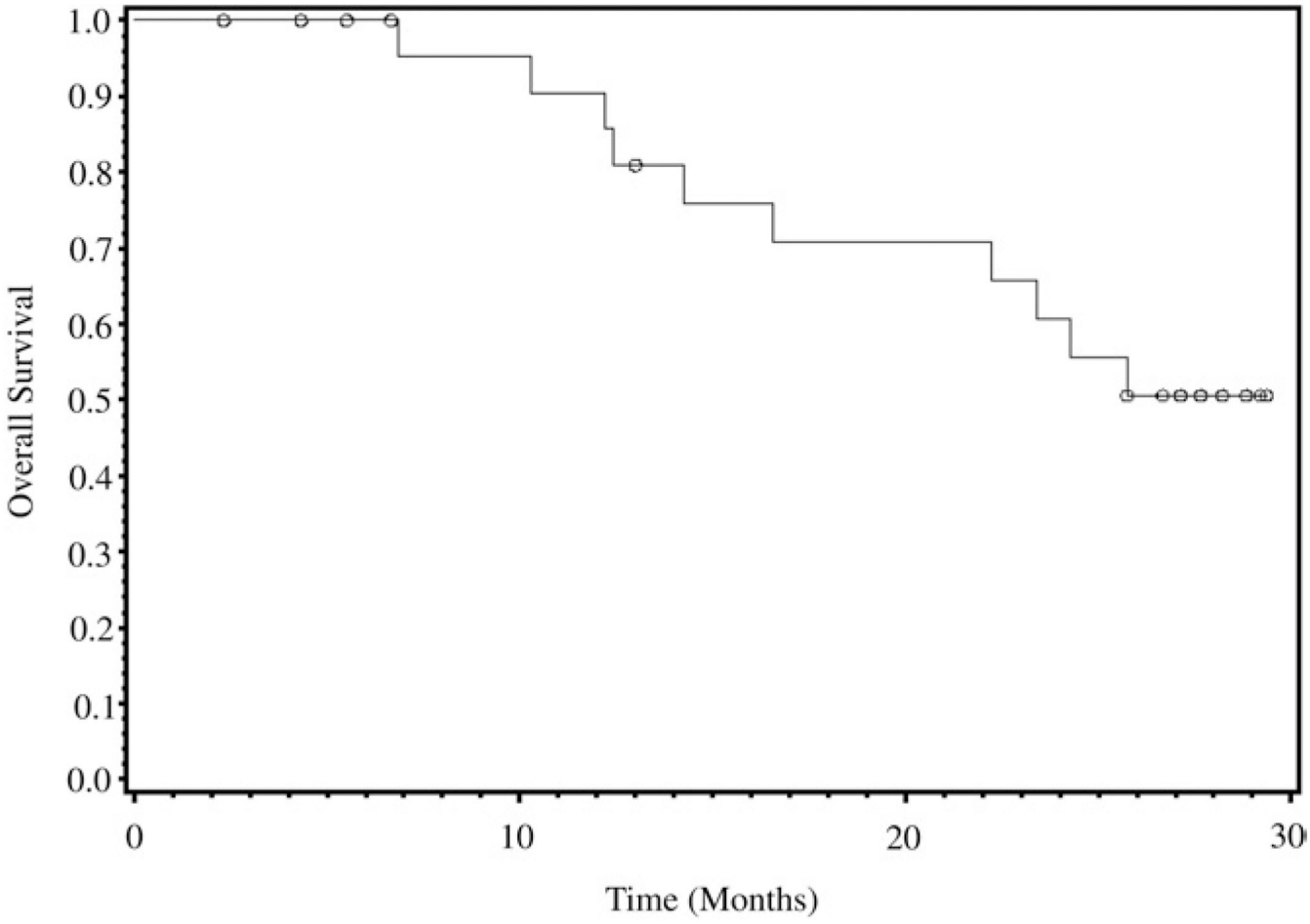

Figure 3.
Kaplan-Meier plot of overall survival

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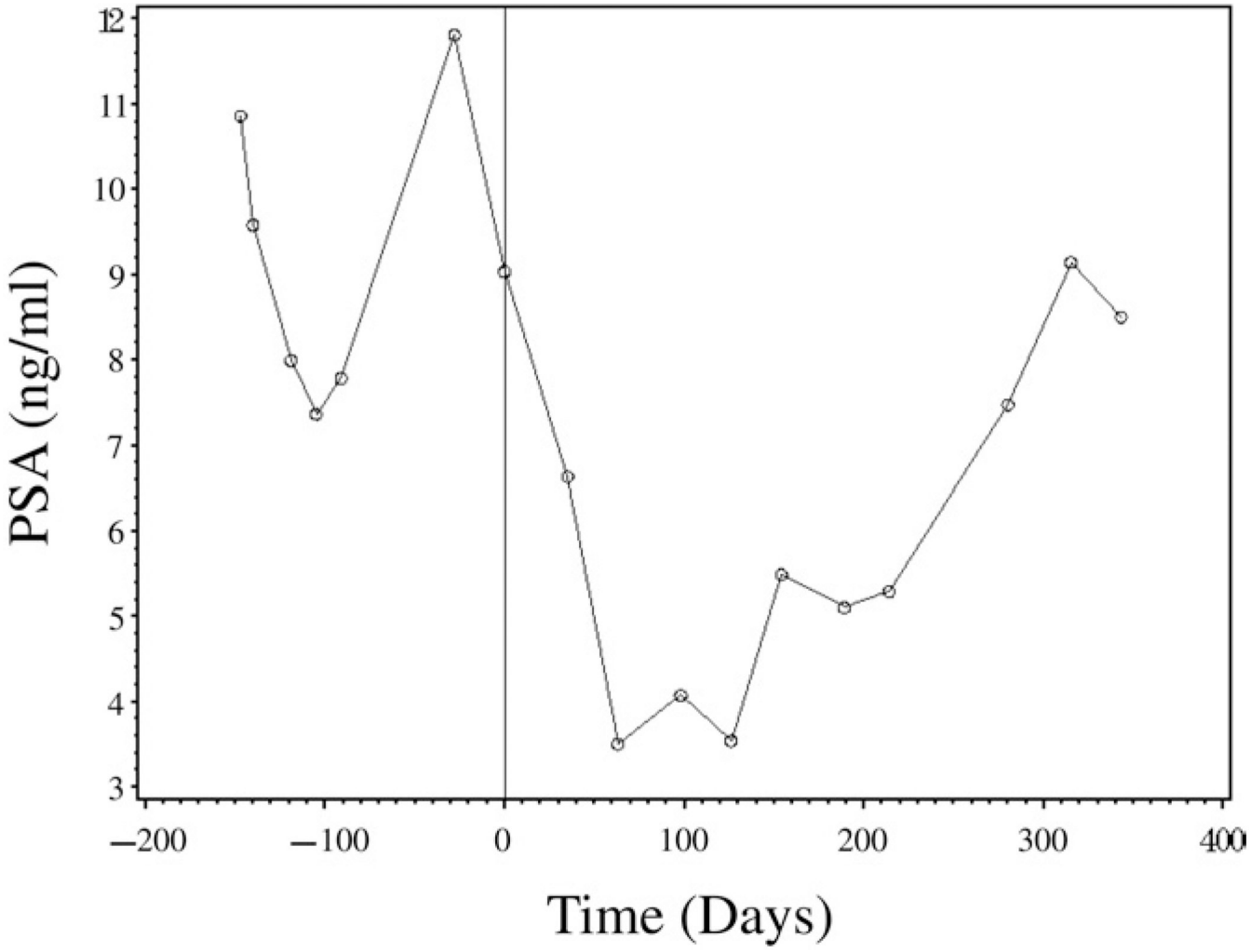

Figure 4.
PSA response to dutasteride for partial responder 1

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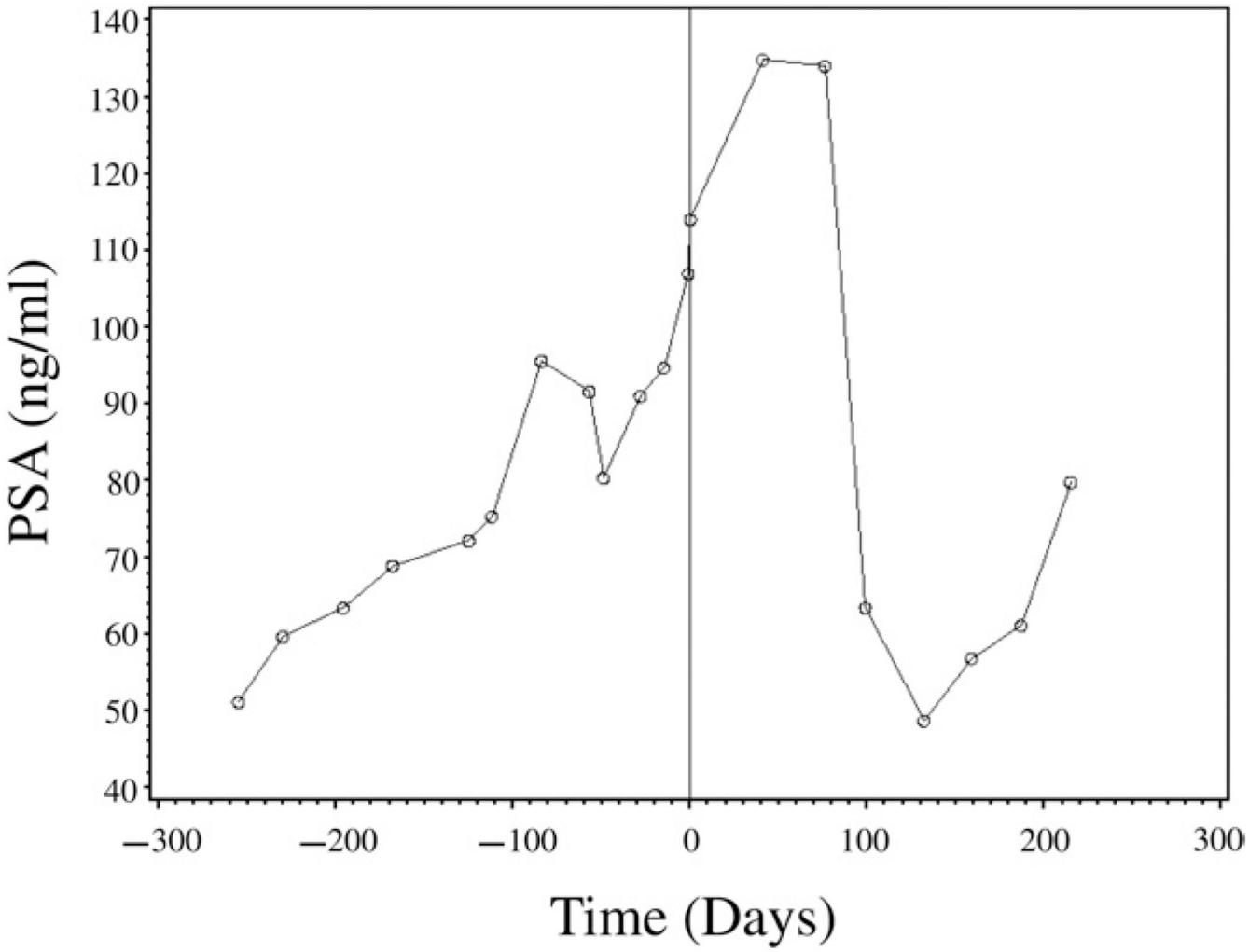

Figure 5.
PSA response to dutasteride for partial responder 2

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Common adverse events

Toxicity	Total No.	No. Grade 1	No. Grade 2	No. Grade 3	No. Grade 4
Hyperglycemia	14	5	7	2	0
Anemia	7	6	0	1	0
Increased alkaline phosphatase	5	4	1	0	0
Hypernatremia	5	5	0	0	0
Fatigue	5	3	2	0	0
Hypokalemia	4	3	0	1	0
Hypoalbuminemia	4	3	1	0	0
Increased aspartate transaminase/alanine aminotransferase	3	3	0	0	0
Hypoglycemia	3	3	0	0	0
Renal insufficiency	2	1	0	1	0
Gross hematuria	1	0	0	1	0
Urine retention	1	0	0	1	0
Deep venous thrombosis	1	0	0	1	0
Stroke	1	0	0	0	1
Ileus	1	0	0	1	0

There were no grade 5 adverse events.