Published in final edited form as:
Prostate Cancer Prostatic Dis. 2013 March ; 16(1): 50–55. doi:10.1038/pcan.2012.20.

A randomized phase II study of pomegranate extract for men with rising PSA following initial therapy for localized prostate cancer

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Abstract

BACKGROUND—Pomegranate juice has been associated with PSA doubling time (PSADT) elongation in a single-arm phase II trial. This study assesses biological activity of two doses of pomegranate extract (POMx) in men with recurrent prostate cancer, using changes in PSADT as the primary outcome.

METHODS—This randomized, multi-center, double-blind phase II, dose-exploring trial randomized men with a rising PSA and without metastases to receive 1 or 3 g of POMx, stratified by baseline PSADT and Gleason score. Patients (104) were enrolled and treated for up to 18 months. The intent-to-treat (ITT) population was 96% white, with median age 74.5 years and median Gleason score 7. This study was designed to detect a 6-month on-study increase in PSADT from baseline in each arm. **RESULTS:** Overall, median PSADT in the ITT population lengthened from 11.9 months at baseline to 18.5 months after treatment (P<0.001). PSADT lengthened in the low-dose group from 11.9 to 18.8 months and 12.2 to 17.5 months in the high-dose group, with no significant difference between dose groups (P=0.554). PSADT increases >100% of baseline were observed in 43% of patients. Declining PSA levels were observed in 13

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CONFLICT OF INTEREST

The corresponding author, Michael Carducci, received $1500 in 2007 from POM Wonderful, LLC, for participating in a discussion of future trials. Harley Liker and Patricia Wozniak are consultants to POM Wonderful, LLC, and Brad Gillespie was, until 2011, the vice president of POM Wonderful. The remaining authors declare no conflict of interest.

patients (13%). In all, 42% of patients discontinued treatment before meeting the protocol-definition of PSA progression, or 18 months, primarily due to a rising PSA. No significant changes occurred in testosterone. Although no clinically significant toxicities were seen, diarrhea was seen in 1.9% and 13.5% of patients in the 1- and 3-g dose groups, respectively.

CONCLUSIONS—POMx treatment was associated with ≥6 month increases in PSADT in both treatment arms without adverse effects. The significance of this on-study slowing of PSADT remains unclear, reinforcing the need for placebo-controlled studies in this patient population.

Keywords

pomegranate; PSA recurrence; PSADT

INTRODUCTION

One-third to one-half of patients who undergo primary therapy for localized prostate cancer (PCA) experience rising PSA levels, an early indication of disease recurrence.[1] For these patients, Gleason scores, the time from local therapy to biochemical recurrence and PSA doubling time (PSADT) predict metastasis-free survival and overall survival.[2–4] The Prostate-Specific Antigen Working Group's guidelines on PSADT concluded that clinical evidence supports PSADT as a predictive factor of clinical progression among post-local therapy PCA patients experiencing biochemical recurrence despite questions as to whether PSADT remains consistent over time.[5,6]

PCA patients with PSA recurrence after local therapy, without evidence of metastatic disease, have treatment options that include radiation in the proper setting, androgen deprivation therapy, or observation, with wide variability in applying these treatments. These patients are ideal candidates for trials of treatments with the goal of delaying development of metastatic disease. They are often open to participation in clinical trials of novel agents, in part to avoid the adverse affects of androgen deprivation therapy.[7,8]

In ongoing research, investigators have focused on the antioxidative effects of polyphenols found in soy, green tea and many fruits and vegetables.[9] Preclinical and clinical studies provide evidence of antiproliferative properties of phytochemical-rich foods such as pomegranate juice.[10] The ellagitannins in pomegranate juice have demonstrated anti-tumor activity *in vitro* and *in vivo* in human PCA cells through downregulation of NF-kB, cyclin-dependent kinases 2/4/6 and Bcl-2 and upregulation of p21/WAF1.[11–14] Recent research demonstrated that pomegranate extract (POMx) also inhibits Akt and mTOR phosphorylation in PCA cells.[15]

In 2006, Pantuck *et al.*[16] published results of a 2-year, phase II clinical trial of pomegranate juice (eight ounces) in PCA patients with a rising PSA after surgery or radiotherapy. Mean PSADT increased from 15.6 months at baseline to 54.7 months following 33 months of therapy.[16] Our study explores a similar end point in a more inclusive biochemical recurrence population, uses POMx capsules instead of juice, and assesses dose response. This randomized, double-blind trial investigates the effects of two doses of POMx on PSADT over 18 months in men with a rising PSA after local therapy. We also report on tolerability and toxicity, compare PSA objective response (≥50% reduction in PSA) between dose groups and assess study compliance.

MATERIALS AND METHODS

Study participants

Study participants were recruited from the medical oncology practice at the Kimmel Comprehensive Cancer Center at Johns Hopkins and from six private urology clinics throughout the US. Participants had histologically confirmed adenocarcinoma of the prostate and had undergone radical prostatectomy or external beam radiation therapy, cryotherapy and/or brachytherapy. Patients were experiencing biochemical recurrence, defined as a rising PSA on ≥3 time points at least a month apart, within 1 year prior to enrollment, and had no radiographic evidence of metastases. Patients with positive lymph nodes on surgical pathology, who were subsequently found to be radiographically free of metastases were allowed on study. Men treated with radical prostatectomy or multiple therapies such as surgery plus radiation were required to have a PSA ≥0.4 ng ml^{-1}. Primary radiation therapy or cryotherapy patients were required to have a PSA >1.5 ng ml^{-1}. Men treated with neoadjuvant hormonal therapy along with external beam radiation were required to have a PSA greater than the nadir plus 2 ng ml^{-1}. There was no upper limit of PSA levels or Gleason score. Men who had therapies that modulate testosterone levels within 1 year prior to the first dose of study medication were excluded, as were patients undergoing concomitant treatment with experimental drugs, high-dose steroids or any other cancer treatment within 4 weeks prior to the first dose of the study product. Participants were included only if they agreed to abstain from commercially available pomegranate products and maintain other dietary supplements at their current dose during the study. Men were excluded if they had Eastern Cooperative Oncology Group performance status >2 or uncontrolled intercurrent illness that limited study compliance. Men were also excluded if they had testosterone <1.5 ng ml^{-1}, white blood cell <3000, absolute neutrophil count <1500, platelet count <100 000, creatinine level >2.5 times upper limit of normal, serum alanine transaminase and aspartate aminotransferase >2.5 times upper limit of normal and/or total bilirubin outside normal limits.

Study design

The study was an 18-month, multi-center, randomized, double-blinded, two-dose trial, powered to detect a 6-month increase in PSADT in an evaluable study population of 80 patients. Participants were stratified by the subject's initial PSADT (≤9 or >9 months) and their Gleason score (≤6 or 3 +4 and 4 +3 or ≥8). The Gleason score was collected at the time of biopsy for radiation patients and prostatectomy for surgical patients. At initial screening, participants underwent medical history and physical examination, pathology review, complete blood count, clinical chemistry panel, fasting lipid panel, urinalysis, concomitant medication assessment, tumor evaluation and measurement of Eastern Cooperative Oncology Group performance status, serum PSA, testosterone, estradiol, sex-hormone-binding globulin, dehydroepiandrosterone, insulin growth factor and androstenedione. Patients were randomly assigned to receive daily dosing of two placebo –plus one capsule of POMx or three capsules of POMx, a pomegranate, *Punica granatum* L, wonderful variety extract. Each POMx capsule contains 1000 mg of polyphenol extract, comparable to about 8 oz of pomegranate juice. Serum PSA, hormones, other chemical and hematological/ laboratory assessments, diet (questionnaire), compliance (diary) and adverse events (interview) were measured quarterly.

The protocol was approved by the institutional review boards at Johns Hopkins and a central institutional review board for each participating site. Each participant gave written informed consent. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v3.0) defined toxicity severity grades. The protocol called for removal of any subject with grade 4 toxicity and delay of therapy for subjects with grade 3 toxicity ≥2

weeks. When grade 2 toxicities occurred, the investigator had the option to continue treatment with careful monitoring or withhold treatment until the values returned to grade ≤1. Other reasons for patient removal include disease progression, withdrawal of consent, non-compliance and investigator judgment.

Study outcomes

The primary objective was to define the effect of two different daily doses of POMx (one or three capsules) on PSADT over 18 months. PSADT computation used the natural log of 2 divided by the slope obtained from fitting a linear regression of the natural log of PSA on time (months). All the available PSA measurements in the year prior to patient enrollment were used to calculate baseline pretreatment PSADT. The post-baseline PSADT was calculated using PSA measurements obtained at baseline and every 3 months during treatment. Patients with no on-study PSA measurements were excluded from the analysis of primary outcome.

A secondary objective was to compare PSA objective response rates, progressive disease rates and stable disease rates between the two arms. Objective PSA response was defined as a decrease of ≥50% in the PSA compared with baseline level, confirmed 6 weeks later. Progressive disease, defined by PSA changes, for patients who achieved ≥50% decline in PSA was defined as an increase in PSA ≥50% over the nadir after at least 6 months on study, confirmed at least 2 weeks later, and minimum PSA rise was >5 ng dl^{-1} or back to pretreatment baseline. For subjects whose PSA had not decreased by 50%, progressive disease was defined as an increase in PSA value ≥50% of baseline or PSA nadir, whichever was lowest, after at least 6 months of treatment, confirmed at least 2 weeks later with a change ≥5 ng dl^{-1}. Stable disease response was defined as any response that did not qualify as objective response or progressive disease.

Progressive disease was also defined as the appearance of radiographically evident metastatic disease and/or physical symptoms felt to be cancer related. In addition, patients not meeting protocol-defined PSA progression came off study upon mutual agreement of physician and patient that progression had occurred. Most commonly, PSA progression was defined with a PSA increase <5 ng/dl (that is, non-protocol defined progression). These patients were not eligible for the open-label extension study.

Statistical analyses

We hypothesized that a paired *t*-test with 80 evaluable patients would yield 94% power to detect a 6-month increase in PSADT from baseline with a s.d. of 15 months. In terms of choosing a more effective daily dose, 40 subjects in each dose group would provide >80% power to detect a 10-month difference in PSADT at a two-sided alpha level of 0.05, also assuming a 15-month s.d.. The target accrual was 100 participants allowing for a dropout rate of 20% to meet the accrual objective of 80 evaluable patients.

A Wilcoxon matched-pairs signed-ranks test and paired *t*-test were used to assess the difference of PSADT on study compared with the baseline for both dose groups combined. The nonparametric test was the primary analysis because the distribution for change in PSADT is highly skewed (non-Gaussian). The change from baseline in PSADT between the two groups was compared using the Wilcoxon rank sum test and the two sample *t*-test.

PSADT was categorized as: (a) <3 months, (b) 3–8.9 months, (c) 9–14.9 months, (d) >15 months or (e) negative slope (that is, decreasing PSA). A shift table showed the number and percentage of subjects with PSADT in each category for baseline and post-baseline PSADT for each treatment group.

Subjects with a negative baseline PSADT (decreasing PSA) were excluded from the analysis of change from baseline to post-baseline PSADT. As has been done previously, subjects with a negative post-baseline PSADT were assigned the largest positive PSADT observed in the study (1532 months), allowing those patients to be included in the intent-to-treat (ITT) analysis.[3]

RESULTS

Participant characteristics

Between October 2007 and December 2008, 104 patients were enrolled and randomly assigned to low- and high-dose POMx groups. May 2010 was 18 months after the last patient enrolled, and data was gathered and the blind was broken in August 2010. Three patients who had no post-baseline PSA measurements were excluded, leaving 101 patients in the ITT. Our analysis is concluded on a modified ITT patient population consisting of 95 patients (46 low and 49 high dose), excluding 6 patients who had declining baseline PSA values (negative PSADT) at baseline. Two additional patients whose PSA did not meet minimum values and one patient taking prohibited medications were excluded from the modified ITT analysis, leaving 92 patients in the evaluable population (45 low and 47 high dose). Age, prior local therapy, Gleason Score, PSADT and other baseline characteristics were similar between the two dose groups (Table 1). Median baseline PSADT was 11.9 and 12.2 for the low- and high-dose groups, respectively.

PSA and PSADT outcomes

The primary end point, median PSADT, for the modified ITT participants increased from 11.9 to 18.5 months ($P<0.001$) with no significant difference between the arms ($P = 0.554$). Median PSADT for patients in the low-dose group increased from 11.9 to 18.8 months ($P<0.001$) and from 12.2 to 17.5 months ($P<0.001$) in the high-dose arm (Table 2).

Objective PSA declines meeting response criterion was seen in 1 out of 46 patients in the low-dose arm and 1 out of 49 patients in the high-dose arm (Table 3). Stable disease was seen in 36 patients (78%) in the low-dose arm and 40 patients (82%) in the high-dose arm. Protocol-defined progressive disease was seen in 9 patients (20%) in the low-dose arm and 8 patients (16%) in the high-dose arm. Despite the low level of objective response, six patients in the low-dose arm and nine patients in the high-dose arm experienced declining post-baseline PSA values.

Figure 1 illustrates the percentage changes in PSADT for the 1-and 3-POMx patient groups using a waterfall plot. In the 1-POMx group, 76% of patients had stable or lengthening PSADT and 46% had ≥100% increase in PSADT. In the 3-POMx group, 82% of patients had stable or lengthening PSADT and 41% had ≥100% increase in PSADT.

Figure 2 illustrates the distribution of patient response by baseline PSADT range. The majority of patients showed movement to slower PSADT ranges: 75% of patients with PSADT <3 months, 61% of patients with PSADT 3 to <9 months and 81% of patients with PSADT 9 to <15 months. In all, 14 patients (14.7%) moved to a faster PSADT range.

Compliance

A total of 92% of patients completed 6 months, 70% completed 12 months, and 36% completed 18 months on treatment, with no significant difference between the two dose groups. In all, 58% of patients (60 patients) completed the double-blind treatment (either completing 18 months or meeting the protocol-defined progression). In all, 42% discontinued treatment before reaching the defined guidelines for discontinuation. One-third

of the patients who discontinued before 12 months met the protocol definition of PSA progression. The most frequent reasons reported for premature discontinuation were non-protocol-defined PSA progression/investigator judgment (15 patients), withdrawn consent (9 patients of whom 6 experienced PSA progression), study-related diarrhea (3 patients) and protocol non-compliance (3 patients). Investigators occasionally reported multiple reasons for discontinuation.

Adverse events

There were no deaths or drug-related serious adverse events reported among the patients. A total of 18 patients had drug-related adverse events, of which 12 were gastrointestinal. diarrhea of grade ≤ 2 was reported in 8 patients (7.7% of total, 1.9% in 1 POMx and 13.5% in 3-POMx) and deemed drug-related in only 5 patients (all 3-POMx). One patient in the 1-POMx group experienced reflux disease and six patients in the 3-POMx group experienced other study-related gastrointestinal adverse events including nausea (four patients) and abdominal pain, constipation, frequent bowel movements, stomach discomfort and vomiting (one patient each). No grade 3–4 clinical chemistry, hematologic or hormonal toxicities were reported. Ten patients experienced cardiac-related adverse events (three in 1-POMx and seven in 3-POMx) such as angina pectoris, arrhythmia and congestive heart failure. None were considered study-drug related; most had been diagnosed with cardiac conditions prior to randomization.

No significant changes were seen in testosterone. Estradiol trended higher in the high-dose group from 28.0 to 32.3 pg ml^{-1}, but not in the low-dose group. The changes in estradiol ranged widely from −37.45 to +38.43 pg ml^{-1} in the low-dose group and from −25.84 to +30.41 pg ml^{-1} in the high-dose group. sex-hormone-binding globulin increased in both groups (42.5–54.7 nmoles l^{-1} in 3-POMx group and 42.8–49.2 nmoles l^{-1} in 1-POMx) with no significant difference between groups.

DISCUSSION

This randomized, phase II, double-blind, dose-finding study compared the effects of two dose levels of POMx on PSA kinetics in men with a rising PSA following radiation or radical pro-statectomy. The study met its primary objective as hypothesized, with a lengthening of PSADT ≥6 months (11.9–18.5 months, P =0.001), with no significant difference between dose groups. PSADT increases were noted by patients across the range of baseline PSADT values, although shortening of PSADT was recorded in 20 (19.8%) patients, as might be expected with a broad patient population. In clinically reviewing patients with shortening of PSADT, none experienced clinical harm. Several transitioned to subsequent treatments and accounted for early withdrawal, moving primarily to androgen deprivation therapy.

The study accrued quickly, in part because patients were disposed to forgo androgen deprivation therapy therapy to avoid associated toxicities.[7,8] The majority of patients stayed on treatment per protocol, but 42% of patients left prematurely over the 18-month study. Patients who left early showed evidence of PSA progression, but often did not meet the protocol definition of a rise of 5 ng dl^{-1}, after 6 months on treatment. Premature departure of patients often reflected investigator and/or patient anxiety concerning disease progression due to rising PSA values, however, 70% of patients remained on study for a year providing adequate on-study PSA values to calculate PSADT reliably. A total of 28 patients in the low-dose arm and 27 patients in the high-dose arm entered the high-dose, open-label extension study and 37 patients remained on study after 18 months of treatment in the open-label extension. Only 8% of patients left the study prior to completing 6 months, and nearly 60% completed protocol, as planned. This level of completion of the 18-month protocol

reflects a disease that continues to progress, and PSA increases can be concerning. When progression occurs, patients frequently ask for access to treatments that could result in a decrease in PSA. Researchers may want to consider shorter trial duration in future studies in this patient population.

These observations of lengthening of PSADT in patients treated with POMx are consistent with the results of the Pantuck *et al.*[16] study of pomegranate juice in a more narrowly defined patient population (0.2<PSA<5 ng ml^{-1}, Gleason score ≤7). At 24 months of treatment, the change from median baseline PSADT to median post-baseline PSADT was 11.5–19.9 versus 11.9– 18.5 months at 18 months treatment in our study. Pantuck's patients were more homogenous and had baseline PSAs ≤5 ng ml^{-1}, whereas 31% of patients in our study had baseline PSA levels >5 ng ml^{-1}, ranging up to 32 ng ml^{-1}. The percentage of patients who had a decreasing PSA on study was roughly similar (18% for Pantuck and 13% in our study). Pantuck's analytical methodology excluded subjects with negative post-baseline PSADT from analysis, thereby underestimating the reported effects. We included any patient with on-study PSA measurements and those coming off quickly may have led to over- or underestimates of the effects of POMx on PSADT. To enable inclusion of all subjects in the ITT population and avoid underestimating the median, we included patients with declining PSA values by converting their negative PSADT to the highest PSADT experienced by study participants, as was done in previous trials.[3,17]

The lack of dose response requires discussion because it may imply that changes in PSADT were not brought about by the compound. An alternative explanation is that the lower dose was sufficient and the higher dose exceeded a threshold for 'drug' activity. Such a result is not uncommon in the use of dietary supplements where dose-limiting toxicities are not found.[18,19] The higher rate of diarrhea in the high-dose group suggests the possibility of reduced absorption and if true, would correlate with decreased bioavailability. However, we did not measure pharma-cokinetics and only 13% of patients in the high-dose group had diarrhea. Therefore, dose-ranging studies like this could benefit from evaluation of bioavailability with markers such as urolithin A, which has been found to be present in urine 24 h after administration of pomegranate juice.[20]

The major limitation of our study is the lack of a placebo arm. A placebo arm was considered, but given the perceived positivity of pomegranate juice, a placebo control was felt to pose difficulties for patient accrual. A dose-response study was an alternative. The US Food and Drug Administration describes dose-response studies as 'one kind of adequate and well-controlled trial that can provide primary clinical evidence of effectiveness' consistent with Code of Federal Regulations Title 21, Section 314.126.[21] In this study, no effect of dose was seen, suggesting that the change in PSADT may be due to chance. Only a placebo-controlled trial could provide the evidence needed to have confidence that the effect was treatment-related. In three prior trials in similar patient populations, patients on the placebo arms experienced substantial lengthening of PSADT while on study. In a Rosiglitazone trial involving 106 patients, 73% of patients on placebo had an increase of PSADT in excess of 100%, and 31% exceeded 200% in PSADT lengthening.[22] In an Atrasentan trial involving 222 patients, 78% of the patients on placebo had a lengthening of PSADT.[23] In a celecoxib trial involving 78 patients, 20% of the patients on placebo had >200% increase of PSADT.[24] In our study, 46% of the low-dose and 41% of the high-dose group showed PSADT increases ≥100%, and 28% and 37%, respectively, exceeded 200%. The high levels of PSADT lengthening seen in placebo arms of prior studies along with the lack of a significant dose-related effect in our study raise the question whether these results could be due to statistical variation and/or placebo effect. Though our study was positive as designed, our results do not definitively show that changes in PSADT can be related to POMx administration. The lack of dose effect that we hypothesized suggests that future studies

should be placebo-controlled and use of low-dose POMx appears appropriate. A phase III, 180 patient, placebo-controlled, 2:1 randomized study of POM juice is maturing (NCT00732043). In addition, a randomized, placebo-controlled, pre-surgical phase II trial involving 70 patients will measure the effects of POMx consumption on oxidative damage, proliferation and localization of urolithins in prostate tissue (NCT00719030).

Variations in measurement of PSA values may contribute to variability in results. Baseline PSADT values were calculated using PSA levels collected at irregular intervals ≥1 month apart within the year prior to study initiation using site-specific laboratories; on-study measurements were obtained consistently every 3 months using a central laboratory. A period of rigorous measurement of PSA values, using a central laboratory, prior to randomization may enable more accurate assessment of baseline PSADT. Further investigation is warranted to illuminate statistical variability in PSA measurement and the placebo effect in trials of therapeutic agents in this patient population.

A related issue is whether changes in PSADT are acceptable end points for clinical trials. Retrospective studies have shown that PSADT is a strong predictor of metastasis-free survival[25] and overall survival[3,26] or both.[4] However, prospective studies are needed to provide confirmation that PSA declines accompanying drug administration correspond with improved metastasis-free survival and overall survival.

No significant changes were seen in testosterone levels, and although significant increases were seen in estradiol in the high-dose group, there was high variability in the measurements. Plants such as pomegranate, which contain phytoestrogens, may raise estrogen levels and theoretically could cause clinically significant estrogenic effects. In this study, estradiol levels fluctuated, sometimes rising just above the reference upper limit of 50 pg ml^{-1} and subsequently declining while still on study, suggesting that the fluctuations were unrelated to the study compound.[27] No clinically significant estrogen-related side effects, such as breast enlargement, were reported. In addition, no significant difference in change in PSADT was seen between the low- and high-dose POMx groups, despite the measurably different increase in estradiol in the high-dose POMx group. In other words, changes in PSADT do not seem to be affected by increases in estradiol. However, given the small sample size, estradiol should be monitored in future studies of POMx.

This randomized, double-blind, dose-finding study in PCA patients with rising PSA attempted to rigorously examine a widely consumed natural product under an Investigational New Drug Application. PSADT lengthened in men on this study, independent of dose level without adverse effects, but questions remain as to causality secondary to POMx. This study confirms the need for placebo-controlled trials when assessing PSADT and ultimately for using clinically meaningful end points such as metastasis-free survival and overall survival before recommending the use of POMx by PCA patients.

Acknowledgments

We thank and appreciate the patients who participated in this study and the many nurses and other health-care providers who assisted with the study. We especially wish to thank the efforts of Ting Wang, Serina King, Rana Sullivan and Susan Hudock at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. Funding for this clinical trial and investigational product were provided by POM Wonderful, LLC, and grant support was provided by an NCI Cancer Center Support Grant (P30) CA 006973.

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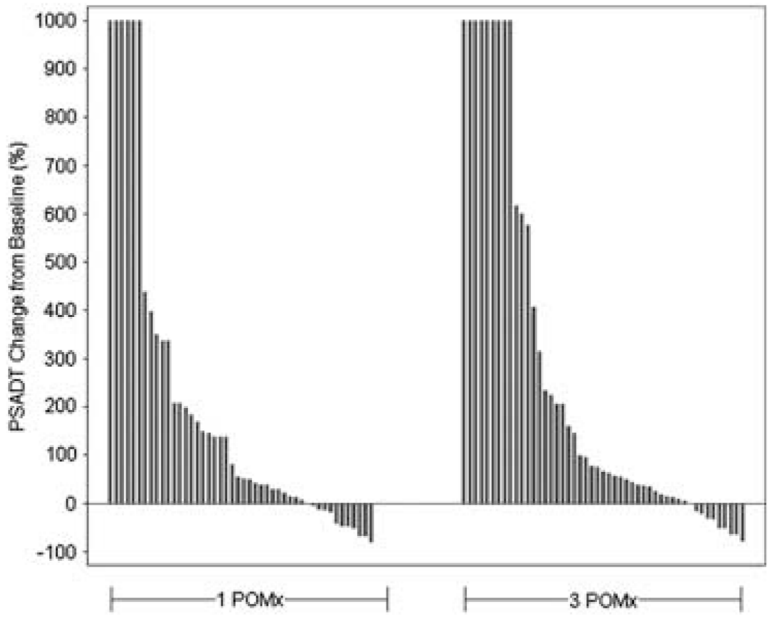

Figure 1.
PSADT percentage change from baseline for each patient in the 1-POMx and 3-POMx treatment groups. (Notes: (1) Patients with negative baseline PSADT were excluded, (2) Patients with negative post-baseline PSADT were assigned the largest observed post-baseline PSADT and (3) Six 1-POMx and nine 3-POMx subjects had PSADT percentage change from baseline >1000%). POMx, pomegranate extract; PSADT, PSA doubling time.

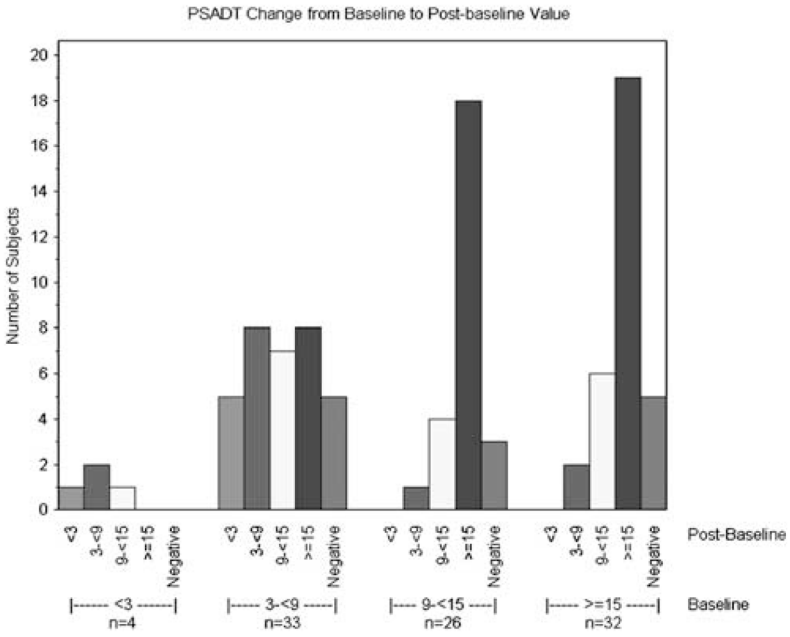

Figure 2.
Number of subjects in each post-baseline PSA doubling time (PSADT) range grouped by baseline PSADT range.

Table 1

Participant characteristics

Characteristic	Double-blind treatment			
	1 POMx, n =50	%	3 POMx, n =51	%
Age (years)				
Mean	71.8		73.5	
Range	51–89		54–92	
Race				
African American	1	2.0%	3	5.9%
White	49	98.0%	48	94.1%
Gleason total score				
Mean	6.4		6.5	
s.d.	1.2		0.9	
Median	7		7	
Range	4–10		4–8	
Baseline PSADT				
≤9 months	14	28.0%	19	37.3%
>9 months	36	72.0%	32	62.7%
Mean	15.1		14.4	
s.d.	12.9		9.5	
Median	11.9		12.2	
Gleason score				
≤6 or 3+4	38	76.0%	38	74.5%
4+3 or ≥8	12	24.0%	13	25.5%
Prior therapies				
Surgery	30	60.0%	22	43.1%
Surgery with radiation	6	12.0%	6	11.8%
Cryotherapy	0	0.0%	2	3.9%
Radiation therapy (XRT)	27	54.0%	27	52.9%
Brachytherapy	9	18.0%	10	19.6%
Anti-androgen deprivation therapy (ADT) with XRT	6	12.0%	7	13.7%
ADT without XRT	5	10.0%	10	19.6%

Abbreviations: POMx, pomegranate extract; PSADT, PSA doubling time.

Table 2

PSADT by treatment group at baseline and post baseline

Treatment	Baseline PSADT (months)	Post-baseline PSADT (months)	P
1 POMx	11.9	18.8	<0.001
3 POMx	12.2	17.5	<0.001
Total	11.9	18.5	<0.001

Abbreviations: POMx, pomegranate extract; PSADT, PSA doubling time.

Table 3

PSA response > 18 months of trial

Treatment	Objective response ≥50% PSA reduction	Stable disease	Progressive disease
1 POMx (95% CI)	1/46 (2%) (0.5–11.5%)	36/46 (78%) (63.6–89.1%)	9/46 (20%) (9.4–33.9%)
3 POMx (95% CI)	1/49 (2%) (0.5–10.9%)	40/49 (82%) (68.0–91.2%)	8/49 (16%) (7.3–29.7%)
Total (95% CI)	2/95 (2%) (0.7–7.4%)	76/95 (80%) (70.5–87.5%)	17/95 (18%) (10.8–27.1%)

Abbreviations: CI, confidence interval; POMx, pomegranate extract.