Phase I trial of exogenous testosterone (T) for the treatment of castrate metastatic prostate cancer (PC). M. J. Morris, W. K. Kelly, S. Slavin, N. Sauter, C. Eicher, K. Regan, T. Curley, A. Delacruz, V. Reuter, H. I. Scher; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Standard treatment for metastatic PC is androgen withdrawal. In preclinical studies, growth of selected PC cell lines and xenografts following prolonged androgen deprivation can be repressed with the re-introduction of high-dose androgens. We conducted a phase I trial to test the feasibility of this strategy in humans. Methods: Eligible patients (pts) had metastatic PC with progression on scans or PSA rises >25% over baseline, had T levels <30 mg/dl, were castrate for ≥1 year, and had failed anti-androgen withdrawal. Pts were treated with T-containing transdermal patches or gel. T was given at 3x standard dosing using three Testoderm TTS 5 mg patches or three AndroGel 1% 5 g packets to maximize serum levels, while GnRH agonists were continued. Three cohorts of 3–6 pts each were defined by treatment duration: 1 week of T, 4 weeks of T, and treatment with T until progression. Antitumor effects were gauged by post-treatment PSA assays and imaging studies. Androgen receptor (AR) levels were assayed from bone marrow specimens to correlate with antitumor effects. Results: Twelve patients were treated, 3 in cohorts 1 and 2, and 6 in cohort 3. No pt was taken off study for tumor flare, defined as an increase in tumor-related symptoms within the first two weeks of therapy. Therapy was well tolerated. There were no grade 4 events, and only 1 grade 3 event (transaminits) was felt to be possibly related to drug. The median total T level achieved by all pts during week 1 was 409 ng/dl (range 95–908), median free T level was 78 ng/dl (range 11–213), and median DHT level was 61 ng/dl (range 29–135). Median treatment duration for cohort 3 was 59 days (range 27–124). AR assays are underway. 1 pt achieved a ≥50% post-treatment PSA decline; 2 pts had stable PSA; no pts had a radiographic response. Conclusions: Administration of T to patients with advanced PC for 1 week, 4 weeks, or until disease progression is safe and not limited by tumor flare. PSA declines were seen, but were rare and short-lived. Combinations of T with other agents that modulate AR may be a more productive strategy than continuous monotherapy. Support: Prostate Cancer Foundation, PepsiCo, Sacerdote Fund, NIH CA102544
In the proceedings of the American Society of Clinical Oncology, Volume 23; 2004; Abstract No. 4560 by Morris, M.J., et al., from Memorial-Sloan Kettering Hospital in New York, the authors describe that in preclinical studies, growth of selected prostate cancer cells following prolonged androgen blockade can be repressed by reintroducing high-dose testosterone. They studied patients with metastatic hormone refractory prostate cancer. They treated them with three times the standard dosing of testosterone in the form of Testoderm patches or AndroGel lotion. Their goal was to maximize serum testosterone levels. They treated 12 patients. No patient had to be taken off study for tumor flare. "Therapy was well tolerated." The median total testosterone level achieved by all patients during week 1 was 409, range 95-908. Median treatment duration for the third cohort of patients treated with 59 days, with a range of 27-124 days. One patient had their PSA decline by greater than 50%. Two additional patients had stable PSA's. Conclusion was "administration of testosterone to patients with advanced prostate cancer for one week, four weeks, or until disease progression is safe and not limited by tumor flare. The authors further stated that "PSA declines were seen, but were rare and short-lived, and suggested that combination therapy may be more productive."
I have described in my high-dose testosterone replacement therapy paper that patients with progressive, metastatic hormone refractory prostate cancer require more than just high-dose testosterone in order to have any significant chance for response. We have patients with this stage prostate cancer and have been on high-dose TRT for years. Additionally, I feel very strongly that most patients require much higher doses of testosterone. My high-dose TRT paper describes studies showing that low doses of testosterone stimulate prostate cancer cells to grow, whereas high doses in a dose-response relationship inhibit the growth of prostate cancer cells. There is a bell-shaped curve response. I believe the authors used far too low a dose of testosterone. Also, they did not use 5-alpha-reductase inhibitors, whereas we always do.

All of our metastatic, hormone refractory prostate cancer patients are also treated with my prostate cancer antiangiogenic cocktail. Our target testosterone level is 1,200-2,500+, a much higher dose than this study utilized. We very rarely lower testosterone doses, even with testosterone levels of 2,500-4,000 if the PSA is stable or declining. I believe that our very different approach for treating metastatic hormone refractory prostate cancer patients explains our superior outcome.