



## SPECIAL BURNING ISSUES SUPPLEMENT APRIL 2007

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### HIGHLIGHTS FROM THE 2007 MULTIDISCIPLINARY PROSTATE CANCER SYMPOSIUM—FEBRUARY 21-24, 2007, ORLANDO, FL

#### ORAL SATRAPLATIN AS SECOND-LINE THERAPY IN ADVANCED PROSTATE CANCER

The investigational drug satraplatin significantly reduced the risk for disease progression in a phase 3 trial in advanced prostate cancer. The oral drug is currently awaiting Food and Drug Administration (FDA) approval.

Satraplatin could offer “a valuable second-line treatment option for men with hormone-refractory prostate cancer,” said lead investigator Daniel Petrylak, MD, from New York Presbyterian Hospital. There are no standard second-line options for these patients at present, he pointed out. Dr. Petrylak was speaking at the Multidisciplinary Prostate Cancer Symposium in Orlando, FL.

An FDA approval application for satraplatin, based on this data, was filed by GPC Biotech Inc. in February. The drug was granted fast-track designation, so it may be available in late 2007.

The phase 3 trial, known as the Satraplatin and Prednisone Against Re-

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#### NEW CLINICAL DATA FOR PROSTASCINT® IN PROSTATE CANCER PRESENTED AT THE 2007 PROSTATE CANCER SYMPOSIUM

Cytogen Corporation (NASDAQ: CYTO) recently reported that clinical investigators from leading cancer research centers presented data from recent and ongoing clinical trials of PROSTASCINT® (capromab pentetide) in prostate cancer. The six PROSTASCINT-related presentations were highlighted by two studies that evaluated the outcomes of prostate cancer patients based on the image findings of PROSTASCINT. The two major studies are summarized below.

Eight-year biochemical disease free survival following permanent prostate brachytherapy with dose escalation in biologic target volumes identified with SPECT/CT capromab pentetide (Abstract No. 357).

This is the first of the two outcomes studies presented related to eight-year survival outcomes data from a prospective, comparative clinical trial using PROSTASCINT fusion imaging. The study utilized PROSTASCINT fusion imaging to assess local and distant disease and to alter the radiation dose to areas of suspected high tumor burden to en-

able more efficient and precise targeting of brachytherapy.

PROSTASCINT fusion imaging combines anatomical images from computed tomography (CT) or magnetic resonance imaging (MRI) with functional images from single-photon emission computed tomography (SPECT) using PROSTASCINT. Data from the study indicate that individualizing seed implantation regimens results in high rates of biochemical disease free survival (bDFS) in these patients.

Importantly, patients whose PROSTASCINT fusion image showed their cancer to be limited to the prostate gland had significantly higher bDFS than those whose image showed uptake outside the prostate. “PROSTASCINT brings a new level of precision to prostate cancer imaging by providing a clearer view of the location and extent of disease in and around the prostate,” said Rodney J. Ellis, M.D., a radiation oncologist and assistant professor of urology with the Case School of Medicine, and the lead investigator in the study.

“Beyond its approved indication in imaging disease, by visualizing the tumor within the prostate gland, PROSTASCINT may help deter-

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## NEW CLINICAL DATA FOR PROSTASCINT® *(continued from page 1)*

mine where to deliver the highest doses of radiotherapy to individual patients -- increasing the chances of disease-free survival while attempting to limit treatment-related side effects," added Dr. Ellis.

The study evaluated the use of PROSTASCINT fusion imaging to define brachytherapy treatment regimens for 239 newly-diagnosed prostate cancer patients. It utilized two sets of criteria for evaluating biochemical failure: the standard ASTRO consensus criteria and the newer Radiation Therapy Oncology Group (RTOG)-ASTRO Phoenix Consensus Conference definition.

Overall, the eight-year bDFS rate was 88.2% using the ASTRO criteria and 82.5% by the Phoenix definition. PROSTASCINT findings of prostate-confined disease correlated with bDFS rates of 91.7%, while patients with periprostatic (near the prostate) and distant disease had bDFS rates of 72.7% and 66.7% by ASTRO criteria ( $p = 0.0003$ ) and were 86.6%, 71.6% and 56.8% ( $p < 0.0001$ ) by Phoenix criteria.

When stratified according to low, intermediate and high risk groups, bDFS rates were 96.1%, 86.0% and 74.2% by ASTRO and 89.8%, 84.1% and 66.2% by Phoenix criteria, respectively.

### **Prediction of prognosis for prostate cancer patients with central abdominal uptake on capromab pentetide (PROSTASCINT) (Abstract No. 173).**

The second outcomes study investigated patients whose PROSTAS-

CINT images showed uptake in the central abdomen as compared to those without such findings. Central abdominal uptake (CAU) of PROSTASCINT is difficult to confirm pathologically; therefore, outcomes in patients with this finding are important.

In the study of 341 men with prostate cancer who underwent PROSTASCINT imaging, PROSTASCINT detected CAU in 69 or 20% of the patients. Patients were followed for a median of four years and prostate cancer-specific death rates were 10 times greater in the CAU group ( $p=0.005$ ). Furthermore, the increased death rates were independent of the use or timing of intervention with hormone therapy.

"Although there has been uncertainty about the meaning of central abdominal activity on these scans, most physicians experienced in the use of PROSTASCINT believe that this multifocal abdominal pattern represents metastatic disease in retroperitoneal and/or mesenteric lymph nodes," said Michael Manyak, MD, vice president of medical affairs with Cytogen.

"This outcomes study is striking because, with limited existing histopathologic correlation, the data show that this pattern of uptake with PROSTASCINT is associated with a poor prognosis. This is now the third study to show a bad prognosis in patients with signal outside of the pelvis, Dr. Manyak Added."

*2007 Prostate Cancer Symposium  
BUSINESS WIRE, 24 February 2007*

## TOREMIFENE MAY EASE ANDROGEN DEPRIVATION COMPLICATIONS

The selective estrogen receptor modulator toremifene (Acapodene) improved lipid profiles and increased bone mineral density (BMD) in androgen deprivation therapy for advanced prostate cancer. So it emerged from a pair of analyses of early interim data from a trial of nearly 1,400 patients, findings that were reported at the 2007 Multidisciplinary Prostate Cancer Symposium by Matthew Smith, MD, PhD, of the Massachusetts General Hospital Cancer Center.

"These interim results suggest that toremifene has the potential not only to reduce the risk of fractures in men with advanced prostate cancer, but also to im-

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## NEW ANDROGEN RECEPTOR TEST MAY PREDICT PROSTATE CANCER AGGRESSIVENESS

Researchers have developed a new tool that may predict whether a patient's prostate cancer will progress after surgery. The tool is the first to measure the amount of androgen receptor protein present in a single cancer cell. Androgen receptors are proteins present in normal as well as cancerous prostate cells, and play a role in prostate cancer progression by acting as binding sites for androgens that fuel cancer growth.

"We have created a highly sensitive predictive test for prostate cancer, similar to those available for breast cancer, that can be used to predict disease progression and potentially impact its course," said Michael Donovan, MD, PhD, Senior Vice President of Research and Development at Aureon Laboratories, Inc., and lead author of the study. "Our data suggest that a high level of androgen receptors in prostate tumors is associated with cancer progression and metastasis."

In this study, researchers used a technique called quantitative immunofluorescence to measure androgen receptors and other molecular markers in prostate tissue from 881 men who had radical prostatectomy at Memorial Sloan-Kettering Cancer Center between 1985 and 2003. They combined the data with clinical variables and image analysis to create a tool for predicting whether a patient's prostate cancer might spread, and how quickly, within five years after surgery.

The researchers found that the tool was 84% accurate in predicting the spread of prostate cancer. The study also found that the risk of cancer progressing increased with an increasing level of androgen receptors in a single prostate cancer cell. The authors note that androgen receptor

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## ANALYSIS FINDS EXTERNAL BEAM RADIATION THERAPY LESS EFFECTIVE THAN RADIOACTIVE SEED IMPLANTS OR SURGERY FOR EARLY PROSTATE CANCER

A new analysis from the Cleveland Clinic found that men who receive external beam radiation therapy (EBRT) for early-stage prostate cancer do not live as long as those treated with radioactive seed implants (brachytherapy, SI) or surgery (radical prostatectomy, RP) to remove the prostate.

The study is the first to assess the effect of the three treatment strategies upon overall survival.

“These findings indicate that the three major forms of treatment for early-stage prostate cancer are not necessarily equivalent in terms of overall survival,” said Jay Ciezki, MD, Staff Physician in the Cleveland Clinic’s Department of Radiation Oncology and the lead author. “Moreover, these findings persisted after controlling for potential confounding factors (age, other illnesses, and smoking history).”

Dr. Ciezki and colleagues analyzed five-year overall survival among 2,285 men with low- or intermediate-risk prostate cancer: 662 men treated with SI, 570 men treated with EBRT, and 1,053 men treated with RP.

All patients were treated at the Cleveland Clinic between 1996 and 2003. The researchers controlled for factors such as Charlson score (a measure of a patient’s general health, including other illnesses), age, smoking status, cardiovascular health, and alcohol use, among others.

After five years, 93.8% of the men who received EBRT were still alive, compared with 95.7% of those who received SI and 97.7% of those who had RP. After controlling for confounding factors, SI and RP were found to be equally effective, while EBRT remained less effective. Smoking, increasing Charlson score, and age were also independently associated with reduced overall survival.

*Abstract # 293 “A Comparison of Overall Survival between Patients with Low and Intermediate-Risk Prostate Cancer Treated with Brachytherapy, External Beam Radiotherapy, or Radical Prostatectomy.” J. P. Ciezki, C. A. Reddy, P. A. Kupelian, et al.*

*2007 Prostate Cancer Symposium  
ASCO press briefing  
24 February 2007*

## ANTISOMA DRUG FOUND EFFECTIVE IN ADVANCED PROSTATE CANCER PHASE II TRIAL

Antisoma, a London based company, announced at the ASCO Prostate Cancer Symposium positive phase II trial interim results in hormone-refractory prostate cancer patients in a combination treatment with AS1404. The results showed that PSA response rates were higher in the AS1404-docetaxel combination (57%) than with docetaxel alone (35%). Time to tumor progression and survival data will be reported later in the year, but current data shows that the frequency of PSA progression was halved in the AS1404-docetaxel combination versus docetaxel alone (17% versus 29%). Safety statistics indicate no significant increase in side-effects from AS1404.

AS1404 (5,6-dimethylxanthenone-4-acetic acid [DMXAA]) is a flavonoid that induces the synthesis of TNF alpha in tumors. This shuts down the tumor vasculature similar to that seen with direct administration of TNF alpha. DMXAA is considered a *vascular disrupting agent since it interferes with the vascular or blood vessels of tumors*. DMXAA has been shown to augment the antitumor effects of melphalan, cisplatin, cyclophosphamide, paclitaxel, radioimmunotherapy, radiation, immunotherapy, and hyperthermia.

*2007 Prostate Cancer Symposium  
Antisoma press release, 24 February 2007*

## SECOND-LINE SATRAPLATIN

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fractory Cancer (SPARC) study, involved 950 patients who had failed on at least 1 prior chemotherapy agent. Dr. Petrylak explained that the trial was designed in 2003, before docetaxel was approved for first-line treatment of prostate cancer, and hence some of these patients had been treated with other agents, including mitoxantrone. All participants received prednisone, a standard therapy for hormone-refractory prostate cancer, and were randomized to receive either satraplatin or placebo.

The primary end point was progression-free survival (PFS), and progression was assessed on a “clinically relevant” composite of radiologic data, skeletal events, symptoms, and death, Dr. Petrylak explained. PFS was significantly increased in the group treated with satraplatin plus prednisone (median PFS, 11.1 weeks) compared with those on prednisone alone (median PFS, 9.7 weeks). The hazard ratio was 0.67 (95% CI, 0.57 – 0.77), which was presented in the ASCO press release as showing a 33% reduction in the risk for disease progression (Prostate Cancer Symposium, Abstract 145, presented February 23, 2007).

“There was a lot of discussion about satraplatin at the symposium this year,” Kevin Kelly, MD, from Yale University, in New Haven, Connecticut, told Medscape. “It did hit its primary end point, and it did show some mild clinical benefits to patients, but the controversy centers on the size of the effect that was seen in this trial — the difference between the median PFS was a total of 10 days, and so the question being asked is whether this is really a benefit.”

Dr. Kelly, who was not connected with the trial, said that he felt there was a benefit from the drug — although the difference in the median time was not large, the survival curves did separate and were continuing to separate. “It seems as patients take the drug longer, they do

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## ANDROGEN DEPRIVATION THERAPY (ADT) MAY INCREASE RISK OF DEATH FROM HEART DISEASE

Researchers from Harvard Medical School have found that ADT for localized prostate cancer may be associated with increased risk of death from heart disease in men aged 65 and older.

“ADT is associated with elevated body mass index, increased body fat deposits, and diabetes, all of which raise the risk of death from heart disease,” explained lead author Henry Tsai, MD, a Resident in the Harvard Radiation Oncology Program. “Although our findings demonstrated that older men receiving this treatment may be at increased risk, even after taking into account other cardiovascular risk factors, a prospective clinical trial would be needed to confirm a cause-and-effect relationship.”

Many men receive ADT in addition to other treatments for localized prostate cancer, with the aim of reducing the level of cancer-fueling testosterone in the body. Drawing from the CaPSURE database, a national registry of men with prostate cancer, Dr. Tsai and colleagues compared cardiac and total mortality between 735 men with localized prostate cancer who received ADT (for 1 to 32.9 months, median duration 4.1 months) and 2,901 men who did not receive ADT.

After controlling for other cardiovascular risks (such as diabetes, hypertension, body mass index, and smoking), the duration of ADT was significantly associated with a shorter time to both death from heart disease and death from all causes. When analyzed by age, the association between ADT use and death remained significant in men age 65 and older, but not in those under age 65. After five years, 3% of older men who received ADT died of cardiac causes, compared with only 0.9% of men who did not.

*Abstract # 298 “Androgen Deprivation Therapy for Prostate Cancer and the Risk of Cardiac Mortality.” H. K. Tsai, A. V. D’Amico, N. Sadetsky, et al.*

*2007 Prostate Cancer Symposium  
ASCO press briefing, 24 February 2007*

## TOREMIFENE & ANDROGEN DEPRIVATION COMPLICATIONS

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prove cholesterol levels, addressing another significant side effect of a standard treatment for this disease,” he said. Androgen deprivation has been shown to decrease bone mineral density and increase fracture risk. It is also associated with increased total cholesterol and a 26% increase in triglycerides, and an increased risk of coronary heart disease.

Toremifene is also being studied for preventing prostate cancer and is marketed under the brand name Fareston for the treatment of breast cancer.

The study recruited 1,392 men ages 50 and older at several centers in the US and Mexico. Participants were randomized to toremifene (80 mg/day) or placebo for two years. Results from first 197 patients completing 12 months of therapy revealed significantly increased BMD at the lumbar spine ( $P<0.001$ ), at the hip ( $P=0.001$ ) and at the femoral neck ( $P=0.009$ ) compared to the placebo group who lost bone at all three sites.

Interim analysis of toremifene’s effects on lipid levels showed:

- An 8% reduction in total cholesterol vs. a 1% decline with placebo ( $P=0.001$ ).
- An 8% decrease in LDL cholesterol vs. a 1% increase with placebo ( $P=0.003$ ).
- A 1% increase in HDL cholesterol vs. a 5% decline in HDL with placebo ( $P=0.018$ ).
- A 13% decrease in triglycerides

## SATRAPLATIN

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better,” Dr. Kelly said.

Dr. Petrylak commented that satraplatin was “very well tolerated.” The most common toxicities were myelosuppression (neutropenia, thrombocytopenia) and gastrointestinal effects (nausea, vomiting), but they were generally mild to moderate. Participants in this trial will continue follow-up to determine overall survival.

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Medscape Medical News, 27 February 2007*

vs. a 7% increase with placebo ( $P=0.009$ ).

- A decrease of 7% in the total cholesterol/HDL cholesterol ratio versus a 6% increase in the placebo group ( $P<0.001$ ).

Dr. Smith cautioned that it was too early to conclude that the changes would result in fewer fractures or cardiac events. Both fracture rate and cardiac events will be evaluated after 24 months of treatment.

“Years ago we were not that concerned about bone loss and lipids because these patients were not expected to have extended survival,” said Kevin Kelly, DO, of the Yale Cancer Center. “But now we are starting to give androgen deprivation therapy for 10 to 15 years,” Dr. Kelly continued. “We are giving it to younger men now for longer periods of time, so these long-term side effects are now becoming more worrisome.”

Dr. Kelly, who was not involved in this study, also cautioned about the possible risks of long-term toremifene treatment. “We don’t know whether these drugs will have similar thrombotic side effects as do other of the selective estrogen receptor modulators,” he said.

*Smith, M. “Toremifene citrate increases bone mineral density in men receiving androgen deprivation therapy for prostate cancer.” Abstract # 149*

*Smith, M. “Toremifene significantly lowers total cholesterol, LDL, and triglycerides and raises HDL in men receiving androgen deprivation therapy for advanced prostate cancer.” Abstract # 15*

*2007 Prostate Cancer Symposium  
MedPage Today, 23 February 2007*

## ANDROGEN RECEPTOR TEST

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levels are an important feature in the predictive model, and that preliminary analyses have suggested that it may play a role in predicting response to hormone therapy.

*2007 Prostate Cancer Symposium  
Press release, 24 February 2007*