PROTOCOL SUBMISSION FORM **Amendment Form**	PROTOCOL NO. 08C0074-F	PRINCIPAL INVESTIGATOR (NIH Employee Name, Inst/Br, Telephone and e-mail): William Dahut NCI MOB 301.435.8183 dahutw@mail.nih.gov

PROTOCOL TITLE: A Phase II Study of Satraplatin and Prednisone in Metastatic Androgen Independent Prostate Cancer (AIPC)

ABBREVIATED TITLE: Satraplatin in Prostate Cancer Reference Number: 314855

Amendment Version Date: 03/11/2011 Amendment Letter: F

The Following revisions were incorporated into this protocol and approved by:

☒ Expedited Review (risk/ benefit ratio not changed)
☐ Full Board Review (meeting date)

Amendment includes changes required by:

☒ N/A
☐ NCI IRB (CCR)
☐ CTEP
☐ Other
☐ Other Sponsor
☐ FDA
☐ Special Studies IRB (DCEG)

If Other, list:

Amendment required Scientific Review?
☐ Yes ☒ No

ADMINISTRATIVE CHANGES

☐ Protocol Title/ Abbreviated Title
☐ New Principal Investigator
☐ NIH Personnel Change
☐ Non-NIH Personnel Change
☐ Converting to multi-institutional trial

DEC clearance required? ☐ Yes ☒ No

Date submitted to IC DEC: N/A Date cleared by IC DEC: N/A

PROTOCOL CONTENT CHANGES

☐ Precis
☐ Study Objectives
☐ Background and Rationale
☒ Eligibility Assessment and Enrollment
☒ Implementation of Study Design
☐ Supportive Care
☐ Accrual Ceiling Changed to: N/A
☐ Data Collection/Evaluation
☐ Human Subject Protections
☒ Data Reporting
☐ Ionizing Radiation Use
☒ Pharmaceutical Information
☐ Appendices

Does the amendment impact the risk/benefit assessment?
☐ Yes ☒ No

INFORMED CONSENT DOCUMENTATION

☐ Text Revisions to Consent(s)
☐ Investigator Contact Information on Consent(s)
☒ No Changes to Consent Form

SIGNATURE
William Dahut - applied signature on 05/13/2011 4:24 PM EDT
New and Old Principal Investigators - electronic signature and date

APPROVALS
Giuseppe Giaccone - applied signature on 05/16/2011 5:08 PM EDT
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Branch Scientific Review Committee Chair - electronic signature and date

Robert Yarchoan - applied signature on 05/17/2011 6:07 PM EDT
Clinical Director- electronic signature and date

Michael Hamilton - applied signature on 05/18/2011 6:09 AM EDT
Chair, IRB Review - electronic signature and date

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NCI Protocol #: 08-C-0074

TITLE: A Phase II Study of Satraplatin and Prednisone in metastatic androgen independent prostate cancer (AIPC)

Abbreviated Title: Satraplatin in Prostate Cancer

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Prior to Day 1

Baseline Evaluation

History and Physical Exam

Laboratory Evaluation

PSA

Electrocardiogram Baseline

Pathologic Confirmation

Tumor Biopsy (if applicable)

Scans:

- CT (chest, abdomen, pelvis)
- Bone Scan
- Chest X-rav

Days 1-5 (Every Cycle)

Anti-emetic, oral administration

Satraplatin 80 mg/m^2 (rounded to the nearest 10), oral administration.

Days 1-35 (Every Cycle)

Prednisone 5 mg, twice daily, oral administration.

(Note* On days 1-5, prednisone will be taken 2 hours prior to Satraplatin dose.)

Every Cycle (+/- 4 days)

Follow- up evaluation

History and Physical Exam

Laboratory evaluation

PSA

Every 2 Cycles (+/- 4 days)

CT Scan (only if baseline CT shows positive disease)

Bone Scan

Every week:

Complete blood count with differential will be drawn (either at the Clinical Center or outside laboratory) for **Cycles 1-3.** If the Absolute Neutrophil Count (ANC) nadir is $\geq$ 1.5 x 10^9/L and the platelet nadir is $\geq$ 100 x 10^9/L, CBC may be drawn only on Day 1 of each cycle starting with **Cycle 4**. If the ANC is $\leq$ 0.5 x 10^9/L and the platelet count is $\leq$ 25.0 x 10^9/L, CBC with differential must be drawn at least 2 times per week or more, until resolved**.**

PRÈCIS

Background:

- Satraplatin is an oral, third-generation platinum analog that has recently been shown to increase PSA decline rates and progression-free survival in hormone-resistant prostate cancer.
- Satraplatin acts by binding to DNA forming intra- and interstrand cross links (DNA adducts), resulting in cell-cycle arrest in G2 phase and eventual apoptosis. One of the mechanisms that bring about resistance to platinum-based chemotherapy is removal of the platinum-DNA adducts by DNA repair pathways, called nucleotide excision repair (NER) and base excision repair (BER) pathways.
- Polymorphisms in the DNA repair genes causing impaired NER and BER capability has recently been shown in some cancers, including head and neck squamous cell carcinoma, non-small cell lung carcinoma, and ovarian carcinoma to predict better treatment outcome and response to platinum treatment.

Objectives:

- Primary objective of this single arm study is to determine if the presence of ERCC1 variant gene polymorphism which is involved with DNA damage repair may be associated with an impact on the progression-free survival of patients with metastatic prostate cancer.
- Secondary objectives of this study includes demonstration of biologic effect by the drug satraplatin in the patient and in the tumor whenever possible, by obtaining tissue biopsy and white blood cell collections, to determine correlation of biologic or clinical effects with PSA progression, evaluate correlations between genotype expression, repair pathways and clinical events, and obtain laboratory correlates which will include pharmacogenetic analysis of prostate cancer patients with genotyping using Polymerase-chain reaction (PCR) followed by either restriction fragment length polymorphism or direct sequencing to genotype single nucleotide polymorphisms of ERCC1, XRCC1, and PARP1.

Eligibility:

- Patients with metastatic androgen-independent prostate cancer
- Had docetaxel-based chemotherapy, but no more than 1 previous cytotoxic chemotherapy line
- Good organ function

Design:

- Phase II trial with single stage design and a planned accrual of 66 patients
- Progression-free survival will be determined using a Fisher's exact test
- Will treat all enrolled patients with oral satraplatin 80 mg/m^2 dose on days 1-5 of every 35-days cycle plus Prednisone 5 mg twice daily every 35 days
- Genotyping will be performed after the first 20 patients to determine if the proportion for wild-type ERCC1 and variants follow a 20:80 split

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1 INTRODUCTION

1.1 Study Objectives

1.1.1 Primary Objective

1.1.1.1 The primary objective of this single arm study is to determine if the presence of ERCC1 variant gene polymorphism which is involved with DNA damage repair may be associated with an impact on the progression-free survival of patients with metastatic prostate cancer.

1.1.2 Secondary Objectives

1.1.2.1 Measurement of overall response rate and overall survival in a post-hoc analysis

1.1.2.2 Demonstrate biologic effect by the drug satraplatin in the patient by white blood cell collections and in the tumor whenever possible, by obtaining tissue biopsy.

1.1.2.3 Determine correlation of biologic or clinical effects with PSA progression.

1.1.2.4 Determine the incidence in this population of AIPC patients of different gene polymorphisms by genotyping using Polymerase-chain reaction (PCR) followed by either restriction fragment length polymorphism or direct sequencing to genotype single nucleotide polymorphisms of ERCC1, XRCC1, and PARP1.

1.1.2.5 Evaluate correlations between genotype expression, repair pathways and clinical events.

1.2 Background and Rationale

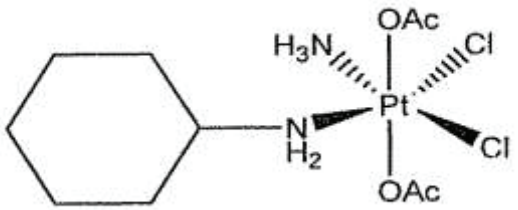
1.2.1 Androgen-Independent Prostate Cancer (AIPC)

Prostate adenocarcinoma is the most common malignancy in American men and the second leading cause of cancer related deaths. 91% of prostate cancer cases are diagnosed while the cancer is still confined to the primary site or after the cancer has spread to regional lymphnodes (localized or regional stage); 5% are diagnosed after the cancer has already metastasized (distant stage).[1] Most patients present with localized disease and undergo potentially curative therapy, either radical prostatectomy (RP) or radiation therapy (RT). Although many men are cured after this therapy, approximately 30,000–50,000 men annually in the United States will develop recurrence after RP.[2-3] For most of these patients, recurrence will be defined by biochemical recurrence (BCR), a rise in PSA with no other documented evidence of recurrence of prostate cancer, otherwise known as D0 stage.[4] Most cases of BCR occur within 10 years of surgery.[5] However, approximately 50% of patients would develop recurrence within four years, at sites distant from the pelvis. [6] Thus they require systemic in addition to local therapy. Several risk factors have been correlated with an increased risk of pBCR. These include pre surgery PSA "velocity", pre-RP PSA, Gleason score, surgical margin status, seminal vesicle invasion, and pathologic stage (i.e., extension of tumor through the prostate capsule).[7] With the identification of active systemic agents, some patients with these risk factors are being enrolled onto trials of adjuvant chemotherapy or RT following RP. Androgen-deprivation therapy is the mainstay of treatment for metastatic prostate cancer but nearly all men with metastatic prostate cancer will progress to an androgen-independent phenotype and exhibit progression of disease.[8-9] Once androgen-independent prostate cancer develops, responses to second-line treatment with alternative hormonal therapy or chemotherapies are limited, with a median overall survival of approximately 12 – 18 months. Androgen-independent prostate cancer(AIPC) causes significant

morbidity, especially with symptoms of pain from bony metastasis and mortality. [10] Chemotherapies have been studied extensively in the field of prostate cancer and has been disappointing until recently with the use of taxanes. Among the first systemic agents studied, mitoxantrone was approved based on symptomatic improvement.[11-12] Subsequently, docetaxel was approved for the treatment of AIPC with the demonstration of improved overall survival of 18.9 months with the use of docetaxel and prednisone over mitoxantrone and prednisone with 16.5 months.[13] The search continues for delivering chemotherapy regimens that yield the best survival outcomes while offering the most palliation in this group of patients where cure is as yet unattainable. It is for this reason that although the combination of docetaxel and estramustine showed similar survival advantage to docetaxel and prednisone,[14] based on fewer side effects, docetaxel and prednisone has become the standard of care in patients with metastatic AIPC. [15] However, the median time to PSA progression with taxane therapy remains limited to about 6-8 months, with many patients progressing thereafter[16]. There is currently little or no options for patients progressing on taxanes. Therefore, there is a clear need for new therapeutic strategies for patients with advanced AIPC who have failed previous taxane chemotherapy.

1.2.2 Satraplatin

Satraplatin [bis-(acetato)-ammine dichloro (cyclohexylamine) platinum IV; formerly known as JM-216] is a third-generation orally available platinum analogue that has similar but improved properties with other platinum agents cisplatin and carboplatin and oxaliplatin.[17] Like other platinum agents, satraplatin exerts its biological activity via reactive biotransformation products that bind to DNA causing the inhibition of DNA replication , cell cycle arrest, and induction of apoptosis. Since their original discovery, platinum compounds (cisplatin, carboplatin, oxaliplatin) have emerged as important agents for the therapy of several human tumors including testicular,[18] bladder,[19] lung,[20] colorectal,[21] head and neck,[22] ovarian,[23] and cervical cancer.[23] The platinum analog satraplatin is of interest as it has shown activity in some platinum resistant tumor models in vitro, and unlike other platinum compounds, it is absorbed when administered orally.[24] This is because the synthesis of the mixed amine platinum (IV) dicarboxylate dichloride series makes satraplatin more lipophilic and more chemically stable than other agents, offering improved oral bioavailability which enables satraplatin to be administered orally. Pre-clinical studies with satraplatin demonstrated cytotoxic and anti-tumor activities comparable to cisplatin or carboplatin.[24] Improved toxicity profiles with nephrotoxicity (as compared with cisplatin) and neurotoxicity(as compared with oxaliplatin) is also obviated with the substitution of the diaminocyclohexane (DACH) with a single cyclohexane. The asymmetrical stable ligands of satraplatin changes its DNA binding properties which results in a potentially different anti-tumor spectrum than that exhibited by cisplatin, carboplatin, and oxaliplatin. [25]



Satraplatin Chemical structure

In Vitro Activity

In vitro studies showed cytotoxic activity in human prostate, ovarian, lung, cervical, colon, renal, CNS, leukemia and melanoma cell lines. In addition, satraplatin and its active metabolite, JM-118, showed encouraging activity in cell lines that have resistance to taxanes, mitoxantrone and cisplatin. Although earlier platinum compounds have shown activity in testicular, ovarian, head and neck, small and non-small cell lung, colon carcinomas, the effectiveness of these compounds were limited because of the inherent problem with resistance. Drug resistance to cisplatin is thought to occur because of decreased accumulation of cisplatin within the target cell, increased detoxification of platinum complexes or due to increased DNA tolerance. Satraplatin and JM-118 were able to overcome this cisplatin resistance by virtue of the mechanisms involving platinum transport and DNA repair process alterations. It was also found that mechanisms which generally confer resistance to non-platinum based chemotherapies tend not to cause cross-resistance with satraplatin. IC_{50} values for in vitro cytotoxicity in three human prostate carcinoma cell lines (the androgen-sensitive LNCaP cell line, the androgen-insensitive PC-3, and Du-145, all at 72 hour exposures using XTT cell viability assay) are summarized in the table below:

	IC_{50} (μM)		
	LNCaP	PC-3	Du-145
Satraplatin	10.9(± 0.6)	1.4(± 0.1)	2.8 (±0.2)
JM-118	0.7 (±0.6)	0.7 (±0.1)	0.9 (±0.2)
JM-383	0.7 (±0.2)	1.1 (±0.2)	1.3 (±0.2)
JM-518	2.2 (±0.7)	1.2 (±0.3)	0.9 (±0.1)
Cisplatin	3.7 (±0.4)	1.0 (±0.2)	1.7 (±0.3)
Oxaliplatin	0.3 (±0.1)	11 (±1.0)	1.8 (±0.5)

Mean(±SD)

Early in vitro data on hormone-dependent LNCaP cell lines showed that treatment with satraplatin for 42 hours with 12 μM resulted in a decrease in cell number (58% and 61% of control, respectively) as well as decrease in PSA protein level (58% and 61% of control, respectively).[26-27] Based on the in-vitro data, PSA may serve as a surrogate marker for clinical response of prostate cancer to satraplatin treatment although this has not yet been confirmed in the clinical setting.

In Vivo activity

In vivo studies have demonstrated antitumor activity of satraplatin against mouse and human tumors transplanted in mice. Satraplatin antitumor activity was maximal when administered orally as a daily x 5 treatment schedule repeated every 21 or 28 days. A similar schedule was adopted for a clinical Phase III study of oral satraplatin plus prednisone called the SPARC (SatraPlatin Against Refractory Cancers) trial. Satraplatin was active in mice bearing subcutaneously implanted hormone-independent human prostate carcinoma (PC-3) tumors when administered orally as two cycles of 5 daily treatment with 3 days-off dose between cycles. Although satraplatin effectiveness increased with increasing dose, these doses were above the

maximum tolerated dose (MTD). The antitumor effect of orally administered satraplatin against five human ovarian carcinoma xenografts (A2780, HX/110, PXN109T/C, SKOV-3 and OVCAR3) was compared with activities of intravenously administered cisplatin and carboplatin.[28-29] Maximal tumor regressions were achieved in the human ovarian carcinoma PXN109T/C model using cycles of 5 daily treatments repeated every 21 or 28 days, as shown in the table below, supporting the selection of a cycling dosing regimen for human clinical trials.[30-31]

Treatment schedule	Dose		Max. BW Loss (%)	Decedents	Max Tumor Regression[a] (Days)
	mg/kg	mg/m2			
Single dose every 21 days	200	600	2.1	0/6	53%(7)
Daily x 5 days,every 21 days	60	180	3.6	1/6	17%(10)
Daily x 5 days,every 28 days	60	180	6.3	1/6	8%(10)
Continuous daily dosing	14	42	14	0/10	74%(7)

BW=Body weight; a=% of the initial tumor volume

Safety Pharmacology and Toxicology

Satraplatin had no significant effects on the hERG channel at concentrations up to 100 μM. In addition, satraplatin had no effect on the electrocardiogram in conscious telemetrized dogs after intraduodenal administration of 22.5mg/kg. Thus, safety pharmacology study data indicate that satraplatin has no potential to cause cardiotoxicity. No functions of the CNS, respiratory, renal and digestive systems were affected by high single doses of satraplatin.

Toxicologic profile in pre-clinical dose-finding toxicity studies showed that the main dose-limiting toxicity were typically hematologic, with neutropenia and thrombocytopenia. Renal toxicity was limited to rats and occurred at a lesser degree compared to cisplatin treatment. Other toxicities include changes in the liver, GI changes in rats, increased mammary adenocarcinomas in rats, decreased spermatogenesis in rats, and increased infections in dogs. [17] Diarrhea may also be dose limiting. No significant cardiac, renal, hepatic, or central nervous system (CNS) toxicity was observed. Nausea, vomiting, and diarrhea were generally mild to moderate, and were controlled with oral anti-emetics and antimotility drugs. The phase I study that most resembles this proposed study with regard to dosing schedule administered satraplatin daily for 14 days. [32] In that study, the dose limiting toxicity was neutropenia, and drug-associated fever that was controlled with acetaminophen was also observed in 32% of patients. The dose of satraplatin that was chosen for later Phase 2 studies consisted of 100 to 120 mg/m^2/day for 5 consecutive days, every 21 or 28 days cycle.

Pharmacokinetics

Satraplatin is a platinum IV complex and the first platinum derivative in clinical development

that is orally absorbed. The pharmacokinetic properties of satraplatin were characterized after oral dosing in Balb/c mice, Sprage Dawley CD rats, Beagle dogs and Cynomolgus monkeys. Pivotal non-clinical pharmacokinetric studies were performed in Sprage Dawley CD rats and Beagle dogs, which were also the primary toxicology species. Platinum was monitored in all biological samples because the presence of platinum is the prerequisite for activity.

The concentration of platinum in plasma ultrafiltrate (PUF) was used as the primary parameter for calculation of satraplatin exposure and for interspecies comparison of satraplatin pharmacokinetics. The concentration of platinum in PUF is a measure of the free (i.e., non-protein bound) platinum concentration. The protein binding of platinum was independent of platinum concentration and irreversible; the fraction bound increased over time up to four hours after oral or intravenous administration to either the rat or the dog and after oral administration to man. Dosage regimen for repeat dose studies in the rat and dog were designed to simulate those utilized in human clinical studies, i.e., one or more cycles of five days of daily oral dosing followed by an off-dose period of 3-4 weeks between cycles. In rats and dogs, after repeated oral doses of satraplatin, the platinum exposure in PUF increased in a dose-related, but not dose proportional manner up to 40 mg/kg (240mg/m^2) and 13.5 mg/kg (270 mg/m^2), respectively. Accumulation factors for platinum in PUF, within a five day dosing cycle, ranged from one (no accumulation) to approximately 1.6.

Pharmacokinetic studies of Satraplatin in humans were also performed with measurement of total plasma platinum and PUF results at a dose of 80 mg/m^2/day as summarized below in both the fed and fasted state:

Table 11.1 Mean (± SD) Plasma and Ultra Filtrate Platinum Pharmacokinetic Parameters During Cycles 1 and 2

PK Parameter (unit)	Day 1, Fasted (n=12)	Day 1, Fed (n=12)	Day 5, Fasted (n=12)
		Plasma Platinum	
C_{max} (ng/mL)	224.9 (50.1)	204.7 (56.6)	568.5 (123.3)
T_{max} (h)[a]	3.5 (2.0-10.0)	7.0 (2.0-12.1)	3.0 (1.0-15.0)
AUC_{0-24} (ng*h/mL)	4204.9 (978.4)	3879.3 (1135.6)	11554.0 (2249.5)
λz (h^{-1})	0.013206 (0.004910)	0.012093 (0.006669)	0.003004 (0.0005274)
$t_{½}$ (h)	99.8 (169.5)	83.7 (62.3)	239.8 (58.0)
		PUF Platinum	
C_{max} (ng/mL)	56.9 (19.2)	42.9 (16.2)	69.4 (26.7)
T_{max} (h)[a]	2.5 (1.0-4.0)	4.0 (1.5-8.0)	1.5 (0.5-8.0)
AUC_{0-24} (ng*h/mL)	466.1 (165.8)	425.3 (112.4)	701.3 (222.1)
λz (h^{-1})	0.034908 (0.014598)	0.052282 (0.020913)	0.003530 (0.0011734)
$t_{½}$ (h)	31.6 (38.0)	16.4 (9.6)	211.9 (55.5)

	Plasma Platinum Accumulation Ratio (%)[b] (95% confidence interval, n=7)	PUF Accumulation Ratio (%) (95% confidence interval, n=12)
AUC_{0-24} (Day 5) / AUC_{0-24} (Day 1)	2.986 (2.578, 3.458)	1.509 (1.374, 1.657)

a. T_{max}: Median (min-max)

b. Cycle 1 patients

Tissue distribution studies were conducted using radiolabeled satraplatin in the mouse and by measurement of platinum in tissues in the mouse, dog and monkey after a single oral dose of satraplatin, and in the rat after single and multiple oral doses of satraplatin. In the rat, platinum was present in most tissues at high concentrations after oral administration of satraplatin. Levels of platinum two hours after the fifth daily oral dose were greater than 1,000ng/g tissue in prostate, bone marrow, kidney, lymph nodes, liver, lung, ovaries and spleen; plasma and PUF platinum concentrations were approximately 800 and 50 ng/ml, respectively. The elimination half-life of platinum from tissues after five days of daily oral dosing was long, i.e., six days or longer.

The half-life in rats has been found to be 15.5 days in whole blood, 4 days in plasma, 6.1 days in PUF; based on urinary excretion was approximately 90 hours. However, pharmacokinetic studies in patients providing accurate estimations of half-life, clearance and volume of distribution were not possible due to the long duration of total plasma platinum concentration observed following satraplatin dosing and the plasma sampling stipulated in the early protocols.

The metabolism of satraplatin and the formation of JM-118 from satraplatin are catalyzed by human CYP450 oxidoreductases. Multiple CYP450s and other NADPH-dependent, reducing enzymes might also be involved in the metabolism of satraplatin. The metabolism of satraplatin is NADPH-dependent in pooled rat, dog and human microsomes and the rate of metabolism of satraplatin is similar in all species. The potential for drug interactions due to induction of

CYP450 isozymes is very low, and thus, satraplatin is not a known inducer of human CYP450 isozymes in vitro. However, satraplatin, but not JM-118, was shown to non-specifically inhibit numerous CYP450 isozymes in vitro. The clinical significance of the inhibition of CYP450 enzymes by satraplatin is unknown.

The majority of platinum was excreted in the urine following intravenous dosing of satraplatin to the mouse, rat and dog. There was a significantly higher recovery of platinum in feces than in urine after oral dosing, however, the increase in fecal recovery after oral dosing is primarily attributable to the excretion of unabsorbed drug.

Other detailed description of nonclinical antitumor activity studies, animal toxicity, nonclinical pharmacokinetics, as well as clinical studies can be found in the Satraplatin Investigator Brochure.[24, 26]

Phase I Single Agent Satraplatin studies

The first phase I clinical trial with the oral agent Satraplatin was initiated in Europe in 1992 using a single dose schedule every 3 weeks. Due to the observed nonlinear absorption with this trial, a 5-day daily dosing was selected for further clinical development. An alternative schedule of two doses given 12 hours apart was then initiated in the UK in 1994 but was terminated prior to achieving maximum tolerated dose (MTD) due to non-liner pharmacokinetics. Toxicity was similar to that occurring in other phase I studies including mild and short-lived nausea, vomiting, and diarrhea, and myelosuppression at the 250 and 350 mg/m^2 dose. Three subsequent phase I studies were initiated (CA-142-002 in the UK, CA142-003/9 in the US, and CA142-012 in Japan) using a 5-daily schedule. Dose-limiting toxicities (DLT) for this schedule was thrombocytopenia, neutropenia, and diarrhea. The MTD dose for Satraplatin given daily for 5 days every 3 weeks ranged from 100 mg/m^{2}day to 140 mg/m$^{2/}$day. The daily for 14 days schedule was also explored in study CA142-007 with the predominant dose-limiting toxicity of myelosuppression. In addition, many patients had retreatment delays because of the late hematologic nadirs. Other reported adverse events included: nausea, vomiting, constipation, stomatitis, somnolence, weight decrease, anorexia, dysphagia, asthenia, fever, headache, pain, insomnia, cough increased, dyspnea, and myalgia. Fourteen patients died within 30 days of their last dose of Satraplatin. Two of these deaths were attributed to study drug toxicity (one due to myelosuppression and one due to unknown causes). In summary, the major DLT observed for the single agent phase I trials were neutropenia, thrombocytopenia and diarrhea. Nausea and vomiting associated with Satraplatin treatment were generally controlled with use of prophylactic antiemetics. Therefore, the initial recommended phase II dosing was daily for 5 days, every 3 to 4 weeks, at a dosage of 100 mg/m$^{2\cdot}$day to 140 mg/m$^{2/}$day. These studies and the DLTs are summarized herein:

Phase I single agent satraplatin studies				
Study No.	**No. of patients**	**Tumor type**	**Satraplatin starting dose (mg/m2/day)**	**Dose limiting toxicity**
CA142-001	31	Solid tumors	60 (single dose)	Not defined

Phase I single agent satraplatin studies				
Study No.	**No. of patients**	**Tumor type**	**Satraplatin starting dose (mg/m2/day)**	**Dose limiting toxicity**
CA142-011	19	Solid tumors	150 (given BID)	Not achieved
CA142-002	32	Solid tumors	30 (daily x 5)	Myelosuppression
CA142-003/9	21	Solid tumors	30 (daily x 5)	Myelosuppression
CA142-012	21	Solid tumors	50 (daily x 5)	Myelosuppression/diarrhea
CA142-007	47	Solid tumors	10 (daily x 14)	Myelosuppression

Clinical Experience: Satraplatin for Prostate Cancer

Eight Phase II trials of single agent satraplatin given daily for 5 days every 3 to 4 weeks have been completed in patients with small cell lung cancer (SCLC), ovarian cancer, non-small cell lung cancer (NSCLC; 2 studies), prostate cancer (2 studies), breast cancer, or gastro-intestinal (GI) cancers. Single agent activity was noted in patients with Small Cell Lung Cancer (SCLC), relapsed ovarian cancer, and prostate cancer.[24]

Satraplatin entered clinical studies in 1992. A phase II trial conducted at multiple US sites accrued 39 patients with HRPC. The starting dose was 120 mg/m^2/day for 5 days, but most patients had the dose reduced to 100 mg/m2/day for 5 days because of excessive toxicity. Among 12 patients with measurable disease, there was one partial response (PR) in a patient with liver lesions, six stable disease (SD), and five patients with progressive disease (PD). Among the 24 patients with PSA responses (defined as a > 50% decrease from the baseline value), there were two complete responses, eight partial responses, and 14 patients with a stable PSA level. The median PSA progression free survival was 33.1 weeks. Analgesic use to determine pain response was not performed, though only 20 patients reported analgesic use at any time during the study. Grade 3/4 neutropenia was reported in 52% of subjects, leukopenia in 41%, and thrombocytopenia in 54%. Another phase II study conducted CA142-026 was a pilot multicenter open-label phase II study designed to evaluate the efficacy and safety of Satraplatin plus prednisone for second-line treatment of patients with HRPC. This study was again terminated as part of the decision of the initial commercial sponsor. At the time of study termination, 10 subjects had been enrolled. Satraplatin was administered daily for 5 days every 28 days at a starting dose of 100 mg/m^2/day and Prednisone 10 mg/day. However, the starting dose of Satraplatin was amended to 80 mg/ m^2/day for 5 days every 35 days due to study drug toxicity – two out of the first four patients treated experienced febrile neutropenia and severe thrombocytopenia on the 100 mg/m^2/day dose. Therefore, the subsequent trials utilized this regimen of 35 day cycles of satraplatin at 80 mg/ m^2/day for 5 days with prednisone 10 mg daily for 35 days. Two phase III trials for patients with HRPC using daily satraplatin (35 day cycles) in combination with orally administered

prednisone were initiated but terminated prematurely as part of a commercial decision of the original pharmaceutical sponsor. The first was a randomized study initiated by the EORTC in June 1998. [33] Patients with symptomatic HRPC were randomized to treatment with satraplatin (100 mg/m^2/day for 5 days every 5 weeks) plus prednisone (10 mg bid daily) (N = 27) or prednisone alone (N=23). All patients have been followed until progression or death. Forty-two patients have died, most due to prostate cancer. A > 50% decrease in PSA was observed in 2/23 (8.7%) on the prednisone alone arm versus 9/27 (33.3%) in the satraplatin + prednisone arm (P=0.046). Toxicity was minimal in both arms; one patient on each arm died due to stomach perforation, most likely related to prednisone. Compliance to treatment was excellent. The median progression-free survival (PFS) was twice as long in the satraplatin + prednisone arm versus the prednisone alone arm (5.2 versus 2.6 months, p=0.023). Median overall survival (OS) also favored the satraplatin arm, 14.9 versus 11.9 months. This difference was not statistically significant, probably due to the small patient numbers. The second trial was a randomized, double blind, placebo-controlled study initiated in December 1998. Fourteen patients with symptomatic HRPC were enrolled and randomized to treatment with either 100 mg/m^2/day satraplatin for 5 days plus BID administration of 10 mg prednisone for 5 days (N = 7), or placebo plus BID administration of 10 mg prednisone alone for 5 days (N = 7) every 5 weeks. Additional details are in the Satraplatin Investigator Brochure.[26]

SPARC (SatraPlatin Against Refractory Cancers) is a Phase III pivotal trial that opened in 2003. It is a multicenter, double-blind, placebo-controlled, randomized Phase III trial assessing satraplatin plus prednisone versus placebo plus prednisone as 2nd line chemotherapy treatment of AIPC. Satraplatin 80 mg/m^2/day or placebo was administered daily on days 1-5 of a 35-day cycle, and prednisone 5 mg was given twice daily on days 1-35 [34] . A total of 950 patients were accrued at more than 200 clinical sites in fifteen countries on four continents. Results from this study show a 40% reduction in the risk of progression, p<0.00001. Hazard Ratio of 0.6 (95% Confidence Interval: 0.5-0.7). The improvement seen in progression-free survival by patients treated with satraplatin increased over time. Progression-free survival at the median (50th percentile) demonstrated a 13% improvement in patients who received satraplatin plus prednisone (11 weeks) compared to patients who received prednisone plus placebo (9.7 weeks). At 6 months, 30% of patients in the satraplatin arm had not progressed, compared to 17% of patients in the control arm. At 12 months, 16% of patients who received satraplatin had not progressed, compared to 7% of patients in the control arm. Pain response was 24.2% for satraplatin and prednisone versus 13.8% for prednisone and placebo (p<0.005) and PSA response was 25.4% for the combination versus 12.4% for prednisone (p<0.01). Overall survival data has not been reported but will be presented at the American Society of Clinical Oncology (ASCO) Meeting in 2007. The treatment dosing regimen used in the SPARC trial will be followed in this proposed Phase II protocol.

1.2.3 Prednisone

Prednisone, a glucocorticoid has been shown to have significant palliative activity in patients with androgen-independent prostate cancer. A previous study was done in patients with androgen-independent prostate cancer, that were given prednisone alone. Patients received 10 mg orally twice a day. Of the 29 patients, 48% of patients had a $\geq$ 25% PSA decline, 34% had a PSA decline $\geq$ 50% and 14% experienced a PSA decline of $\geq$ 75%. The average PSA declined in this study population was 33%. Average progression free survival was 2.8 months.[35] Prednisone has also been used with satraplatin in the previous EORTC Phase III trial as well as the recently concluded SPARC trial discussed in section 1.2.2.

1.2.4 Background on DNA gene polymorphisms and rationale for use of satraplatin in AIPC

Satraplatin forms the same DNA adducts as cisplatin but retains a unique carrier ligand. Platinum agents, with cisplatin as the prototype, have been in use for several decades and constitute the backbone of treatment for several malignancies. Its main cytotoxic function has been based on the formation of mono- and bi-functional adducts in the DNA, which cause inter-/intrastrand cross linking. One mechanism by which tumors develop resistance is by increased tolerance to DNA damage as a result of a highly efficient DNA repair capacity.[36] Understanding of the multiple enzymatic pathways leading to repair of nonspecific DNA damage has been elucidated with the Nucleotide excision repair (NER) and Base excision repair (BER) systems. Many studies have indicated that polymorphic DNA repair genes influence platinum-based chemotherapy in a cancer-specific manner. It has been hypothesized that impaired NER/BER function led to decreased capacity for DNA repair of the tumors following treatment with cisplatin, leading to greater DNA damage, and ultimately cell death. [37-38] It also confers a higher risk for cancer because of the suboptimal DNA repair capability. In particular, NER capability as measured by a plasmid-based host reactivation assay was significantly lower in prostate cancer cases. Using cryopreserved lymphocytes collected from a clinic-based case-control study, results showed that the mean NER capacity was significantly lower (P = 0.03) in 140 cases (mean +/- SD, 8.06 +/- 5.17) than in 96 controls (9.64 +/- 5.49). There was a significant association between below-median NER capacity and prostate cancer risk: odds ratio (OR), 2.14; 95% confidence interval (CI), 1.19-3.86, after adjustment for age, race/ethnicity, smoking history, benign prostatic hyperplasia, and family history, supporting the hypothesis that a deficient NER capacity results in increased risk for prostate cancer. [39] Several key and rate-limiting enzymes including ERCC1, XRCC1 have been studied and have increasingly been used to predict response to chemotherapy in several cancers such as squamous cell carcinoma of the head and neck,[40], Non-small cell lung cancer,[41] and ovarian cancer. [42] .Single nucleotide polymorphisms (SNPs) in a given gene may affect the function of the encoded protein and preclinical data suggest that one polymorphism at the ERCC1 gene (C8092A) may affect its mRNA stability, resulting in impaired DNA repair capacity.[43] Evaluation of tumor specimens for expression of DNA repair genes may predict for response to platinum and ultimately, for survival. In the IALT Bio study that looked at 761 tumor specimens, a benefit from cisplatin-based adjuvant chemotherapy was associated with the absence of ERCC1 (test for interaction, P=0.009) [44]. This forms the basis for obtaining tumor biopsy specimens from prostate cancer patients in this study, especially since specific gene polymorphisms has not been extensively studied in prostate cancer [45]Since satraplatin DNA-adducts are efficiently repaired by mammalian NER pathway,[46] and less likely recognized by mismatch repair mechanism, [47] or post-replication repair mechanism,[48] it would be plausible that the same gene polymorphisms that give rise to impaired NER pathway would confer better response to satraplatin in patients with prostate cancer.

1.2.5 Excision repair cross-complementation group 1 (ERCC1)

ERCC1 forms a heterodimer with XPF and as a unit, they perform the 5’ incision which is specific to excision of Pt-DNA adducts.[49] Greater levels of total ERCC1 mRNA and full length ERCC1 mRNA were found in ovarian cancer tissues resistant to platinum-based chemotherapy.[42] The most widely studied polymorphism is 19007C>T (Asn118Asn), in which

the variant T allele was correlated to better response to platinum-based chemotherapy in epithelial ovarian cancer.[50] and oxaliplatin/5-FU combination chemotherapy in advanced colorectal cancer. [51] Another common SNP in ERCC1 is 8092C>A in 3' UTR. It was suggested that this variant may affect its mRNA stability which in turn results in reduced protein activity.[43] The variant A allele increased gastrointestinal toxicity in platinum treated NSCLC patients.[52] We have found that the ERCC1 N118N variant may occur at a lower frequency (around 20%) among African-Americans (unpublished data). It is unclear how this relates to the higher incidence of prostate cancer that is found in African-Americans. The frequency of the more widely studied polymorphism ERCC1N118N wild-type is also found to occur at around 20%, while variant alleles are about 80% (49% for the CT variant allele and 30% for the TT variant allele), in control groups of Caucasian men.. (unpublished data, please see Table on summary of key findings on variant DNA repair genes). Using these data, we propose that prostate cancer patients exhibiting ERCC1 variant alleles may have better response to a platinum agent such as satraplatin.

Table on summary of key findings on variant DNA repair genes in Caucasians and African-Americans (unpublished data)

Single Nucleotide Polymorphism	Genotype	Caucasian Counts (freq.)	African American Counts (freq.)	P VALUE
ERCC1N118N	CC CT TT TOTAL	23(0.21) 53(0.49) 32(0.30) 108	96(0.76) 27(0.21) 4(0.03) 127	<0.001
ERCC1 C8092A	CC AC AA TOTAL	77(0.53) 59(0.40) 10(0.07) 146	74(0.52) 56(0.40) 11(0.08) 141	N.S
ERCC2 K751Q	AA AC CC TOTAL	49(0.42) 56(0.47) 13(0.11) 118	81(0.56) 57(0.40) 6(0.04) 144	<0.001
XRCC1 R399Q	GG AG AA TOTAL	49(0.46) 47(0.44) 10(0.10) 106	113(0.80) 26(0.19) 2(0.01) 141	<0.001
XRCC1 R194W	CC CT TT TOTAL	120(0.87) 17(0.12) 1(0.01) 138	133(0.90) 14(0.09) 1(0.01) 148	N.S

Single Nucleotide Polymorphism	Genotype	Caucasian Counts (freq.)	African American Counts (freq.)	P VALUE
PARP1 V762A	TT CT CC TOTAL	80(0.67) 32(0.27) 7(0.06) 119	108(0.91) 11(0.09) 0(0) 119	<0.001 (ALLELE FREQ.)

1.2.6 Other DNA repair gene polymorphisms

Xeroderma pigmentosum group D: XPD gene, also known as ERCC2, encodes for a DNA helicase which catalyzes another rate-limiting step in NER pathway. A sibling-based study on prostate cancer correlated the variant homozygotes of Asp312Asn to slightly higher risk of prostate cancer and the variant allele of XRCC1 Arg399Gln adds great value to this effect [53]. And a most recent study showed that combined genotypes with at least one variant allele in XPD Lys751Gln and XRCC1 Arg399Gln were strongly related to improved survival in bladder cancer patients treated with platinum-based chemoradiotherapy [54]. However, some discrepant results were found in XPD polymorphisms with relationship to platinum chemotherapy. Possessing the wild-type allele of Lys751Gln increased the risk of suboptimal DNA repair though the Asp312Asn polymorphism were not found to affect DNA repair activity [55]. The wild-type allele Lys751Gln was associated with better response and longer survival in colorectal cancer patients received 5-fluorouracil/oxaliplatin chemotherapy, and this allele was in a strong linkage with Asp312Asn [56]. In addition, the variant allele of Asp312Asn was related to decreased overall survival, especially when combined with variant allele of XRCC1 Arg399Gln, in NSCLC patients treated with cisplatin/carboplatin [41].

Besides the NER pathways, other DNA repair proteins involved in base excision repair (BER) pathway, such as XRCC1 and PARP1 were also considered important because of their potential activities in removing platinum-DNA adducts.

X-Ray cross complementation group 1: XRCC1 is a principle player in BER pathway. It stimulates endonuclease activities following the excision of a damaged base and acts as both a scaffold and a regulator for other BER proteins [57]. The Arg399Gln change residues were firstly identified by Shen et al. This polymorphism resides in the C-terminal side of PARP-interacting domain [43]. The wild-type allele of Arg399Gln appeared more frequently in good responders to platinum-based chemotherapy in bulky cervical cancer patients [58]. Advanced colorectal cancer patients carrying variant allele of this substitution were more resistant to oxaliplatin/5-FU chemotherapy [59]. In addition, high expression levels of XRCC1 were found in bladder cancer patients with improved survivals following radical radiotherapy [60]. Published data have also shown correlations between the variant allele of Arg194Trp and increased risk of lung cancer [61], oral squamous cell carcinoma [62], and better response to platinum-based chemotherapy in advanced NSCLC [63].

Poly (ADP-ribose) polymerase-1: PARP1 is another member of BER complex and serves in detecting DNA interruptions. In response to these breaks, it recruits XRCC1 and other partners for further processing of the damages [64]. Overexpression of XRCC1 dramatically decreased PARP1 activity in vivo [64]. The variant allele of Val762Ala contributed to significantly lower PARP1 activity and increased prostate cancer risk [65]. Furthermore, PARP1 inhibitor was

proved to be able to increase the sensitivity of platinum compounds against platinum resistant ovarian tumor cells [66].

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 Eligibility Criteria

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histopathological confirmation of prostate cancer by the Laboratory of Pathology of the NCI or Pathology Department of the National Naval Medical Center or Walter Reed Army Medical Center prior to entering this study. Patients whose pathology specimens are not available may be enrolled in the trial if the patient has a clinical course consistent with prostate cancer and available documentation from an outside pathology laboratory of the diagnosis. In cases where original tissue blocks or archival biopsy material is available, all efforts should be made to have the material forwarded to the research team for use in correlative studies.

2.1.1.2 Patients must have metastatic progressive androgen-independent prostate cancer. There must be radiographic evidence of disease (by CT scan or bone scan) after primary treatment that has continued to progress despite hormonal agents. Progression requires that a measurable lesion is expanding, new lesions have appeared, and/or that PSA is continuing to rise on successive measurements. Patients must have progressive disease after receiving 1 prior docetaxel-based cytotoxic chemotherapy. Patients on flutamide for the prior 6 months must have disease progression at least 4 weeks after withdrawal. Patients on bicalutamide or nilutamide must have progression at least 6 weeks after withdrawal.

2.1.1.3 Patients may only have received 1 prior cytotoxic chemotherapy. For the purpose of this study, multiple courses of a taxane-based regimen may count as a single regimen. Multiple courses of a non-taxane agent or a combination chemotherapy regimen, administered in a similar fashion may count as a single regimen.

2.1.1.4 Patients must have a life expectancy of more than 3 months.

2.1.1.5 Patients must have a performance status of 0 to 2 according to the ECOG criteria.

2.1.1.6 Patients must have adequate organ function as defined below:

Leukocytes	$\geq$3,000/μl
Absolute Neutrophil Count	$\geq$1,500/μl
Platelets	$\geq$100,000/μl
Total bilirubin	$\leq$1.5 X institutional upper limits of normal*
AST(SGOT) and ALT(SGPT)	$\leq$2.5 X institutional upper limit of normal
creatinine OR Creatinine clearance	$\leq$1.5 X institutional upper limits of normal $\geq$60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

*Except patients with Gilbert's disease who may proceed despite elevated total bilirubin

2.1.1.7 Patients must have recovered from any acute toxicity related to prior therapy, including surgery. Toxicity should be $\leq$ grade 1 or returned to baseline.

2.1.1.8 Hormonal profile: all patients who have not undergone bilateral surgical castration must continue suppression of testosterone production by appropriate usage of GnRH agonists.

2.1.1.9 Patients must not have any ongoing malignancies requiring active therapy.

2.1.1.10 Patients must be able to understand and sign an informed consent form.

2.1.1.11 Concurrent use of bisphosphonates will be allowed if patients have previously been on it; if patients are not on bisphosphonates at the time of study enrollment, bisphosphonates may be started at cycle 2.

2.1.1.12 Patients who require hematopoietic growth factor support (e.g. epogen, darbepoetin), but not myeloid growth factors (except after cycle 1 day 1 if clinically indicated), NSAIDs, and other maintenance medications prior to study entry will be allowed to continue their supportive therapies.

2.1.1.13 Results from embryo-fetal development indicated that satraplatin should be considered a teratogen in women of childbearing potential and hazardous in respect to spermatogenesis for men. For this reason, men must agree to use adequate contraception (abstinence; hormonal or barrier method of birth control) prior to study entry and for the duration of study participation.

2.1.1.14 Patients must be able to swallow capsules

2.1.1.15 Patients on chronic stable steroids (equivalent to no more than 10 mg of prednisone daily dose) used for non-cancer treatment may be allowed on study

2.1.2 Exclusion Criteria

2.1.2.1 Patients who have had prior treatment with satraplatin or other platinum containing compounds will be excluded.

2.1.2.2 Patient**s** may not be receiving any other investigational agents.

2.1.2.3 Patients with known active brain metastases are excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

2.1.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to satraplatin or prednisone.

2.1.2.5 Uncontrolled intercurrent illness including, but not limited to ongoing or active serious infection, symptomatic congestive heart failure, unstable angina pectoris, or psychiatric illness/social situations that would limit patient compliance with study requirements.

2.1.2.6 Prior radiation therapy to > 30% of the bone marrow, or who have received strontium-89, rehenium-186, or rhenium-188 will be excluded from this trial. Patients who have received prior radiotherapy must have recovered from acute toxicity due to radiation. Patients who have received samarium-153 are eligible for the study because samarium has a significantly reduced half-life compared to aforementioned isotopes.

2.1.2.7 Patients with immune deficiency are at increased risk of lethal infections when treated with marrow-suppressive therapy. Therefore, HIV-positive patients are excluded from the study.

2.1.2.8 Patients with a history of major gastrointestinal surgery or pathology likely to influence absorption of oral medications, like bypass surgeries, Whipple's procedure, or any surgery that would impair reliable absorption of oral drugs.

2.1.2.9 Patients with a disease where corticosteroids are contraindicated, e.g. active gastric or duodenal ulcer, or poorly controlled insulin dependent diabetes. Patients with well-controlled insulin-dependent diabetes mellitus may be considered, providing they understand their glucose levels will increase, and their insulin dose will require adjusting.

2.1.2.10 Because no dosing or adverse event data are currently available on the use of satraplatin in patients <18 years of age, children are excluded from this study.

2.2 Research Eligibility Evaluation

2.2.1 Imaging Studies (Baseline- obtained within 4 weeks prior to enrollment):

- Technetium-99 Bone Scintigraphy,
- Chest X-ray,
- CT scan of chest, abdomen and pelvis

2.2.2 Laboratory Evaluation (Baseline- obtained within 16 days prior to enrollment)

- Hematological Profile: CBC with differential and platelet count, PT, aPTT, fibrinogen.
- Biochemical Profile: electrolytes, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, calcium, phosphorus, albumin, magnesium, uric acid, total protein, glucose, albumin, amylase, lipase, testosterone level.
- PSA (baseline within 7 days prior to enrollment)
- Electrocardiogram (performed within 21 days prior to enrollment); Patients with a history of myocardial infarction or cardiac arrhythmias will undergo evaluation by cardiology.

2.3 Patient Registration

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://intranet.cancer.gov/ccr/welcome.htm) must be completed and faxed to 301-480-0757. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail. Please note, it is very important for all registrars to acquire encrypted e-mail from NIH Help Desk, since the verification of registration includes patient's information. A recorder is available during non-working hours.

3 Study Design

This trial will be conducted using a single stage design. However, to protect against the unlikely possibility that the agent will be associated with overall progression free survival which is substantially below what is expected based on results from other trials, an early stopping rule will be implemented as follows. After 20 patients have been enrolled and 6 months have passed since the 20th patient has enrolled, the proportion of patients who have attained 6 months without progression will be determined. If this fraction is no greater than 3/20 (15% who have attained 6 month progression free survival), then the trial will cease enrolling further patients because a one-sided 90% upper confidence bound on 3/20 is 30.4%, which would only indicate at best a modest probability of marginal consistency with what would be expected as the overall outcome using satraplatin. Similarly, genotyping for ERCC1 will also be performed after the 20th patient to test whether we are achieving the true probability of ERCC1 wild type proportion of 20% as indicated in earlier studies (in Caucasians). If the true probability is as shown, the probability of having 0 or 1 with WT genotype is tabled:

True WT proportion	Probability of getting 0 or 1 with WT
0.2	7%
0.1	39%
0.05	74%

Thus, if only 0 or 1 patient out of the first 20 patients should have ERCC1 WT genotype, then this would be more consistent with a 0.05 rather than a 0.20 true rate of WT. If this turns out to be the case, then we would re-evaluate the procedure for enrolling subjects to try to increase the proportion of patients with ERCC1 WT and amend the protocol accordingly. Otherwise, accrual to the full 66 patients will continue. See section 9.. Statistical analysis for further review of statistical design.

3.1 Drug Administration

3.1.1 Satraplatin administration

Satraplatin will be administered in an outpatient basis. This is to allow for pharmacokinetic samples to be obtained as outlined in section 3.4.1.1. Reported adverse events and potential risks are described in Section 6. Appropriate dose modifications for satraplatin are described in Section 3.3. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Satraplatin is supplied as 1 x 5 capsules in blister strips. There are two strengths of capsules, one with 10 mg dose and the other with 50 mg dose. Patient's dose will be calculated based on body surface area as 80 mg/m^2 dose to be given daily x 5 days, every 35-days cycle. The total dose of satraplatin delivered should be rounded to the nearest 10 mg dose, (i.e., if total dose is < 165 mg, deliver 160 mg; if total dose > or = 165 mg, deliver 170 mg) after calculation of patient BSA. Patients are to swallow the capsules whole with approximately 125 ml - 250 ml of any clear liquids. Capsules should be taken on an empty stomach (no food for 2 hours before or 1 hour after dosing). Satraplatin will be given as self-administered oral doses of 80 mg/m^2 for days 1-5 every 35 days. Patients will be asked to maintain a diary to document consumption of satraplatin

as outlined in section 8 and Appendix B.

Patients will be required to have weekly blood counts drawn for the first 3 cycles of the study at an outside laboratory or at the Clinical Center given the risk of decreased white cell count and platelet count from satraplatin.

3.1.2 Prednisone administration

Prednisone 5 mg will be administered two hours prior to satraplatin (along with antiemetic, outlined in section 4.2) in AM and another 5 mg of prednisone in PM, on days 1-5. On days 6-35, patients will continue Prednisone 5 mg twice daily. Therefore, prednisone is given continuously twice daily throughout the 35-day cycle.

3.2 Treatment Modifications

Toxicities will be described using the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3). The following adjustment will only apply if the toxicities reported are attributed by the investigator to be related to satraplatin and prednisone therapy.

3.2.1 Dose modification for satraplatin:

Dose reductions will be according to the following rules for satraplatin:
For Grade 1 toxicity, no treatment interruption or dose reduction for either satraplatin or prednisone, will be made. For Grade 2 or greater toxicity, subsequent treatment with satraplatin will be followed as shown in the table below and following the dose reduction schema.

Non-Hematologic toxicity Dose adjustments and reductions		
Grade of Non-hematologic toxicity (CTCAE v3.0)	Management/dose adjustment	Dose reduction
Grade 1	None	None
Grade 2 nausea, vomiting or diarrhea	Maintain dosing with symptomatic treatment; Repeat dosing if all tablets appear in emesis	None
Persistent Grade 2 nausea, vomiting or diarrhea despite symptomatic treatment that remains unacceptable (intolerable) to the patient	Decrease from 80mg/m2 to 60 mg/m^2**	Decrease by 20 mg/m^2

Non-Hematologic toxicity Dose adjustments and reductions		
Grade of Non-hematologic toxicity (CTCAE v3.0)	Management/dose adjustment	Dose reduction
Grade 3 clinical, Grade 3 or 4 laboratory abnormalities which are associated with clinical signs and symptoms that are felt to be drug-related	Hold satraplatin and reevaluate the patient at least weekly until toxicity improves to ≤ Grade 1 or pre-treatment baseline*	Decrease by 20 mg/m^2 (i.e., if patient is at $80mg/m^2$/day dose, decrease to $60mg/m^2$/day)**
Grade 4 clinical (except pulmonary embolism without significant hypoxia and hemodynamic instability)	Off-study	
Grade 4 vomiting or diarrhea that can not be controlled by medical treatment and that occurs after one dose reduction	Off-study	

*Treatment delay should not be >8 weeks from Day 1 of prior cycle or >3 weeks from the start of next scheduled cycle; otherwise, patient will be taken off-treatment.

**If patient is already at $60mg/m^2$, decrease further to $40mg/m^2$; No further dose reduction after $40mg/m^2$ will be permitted

-Non-hematologic toxicity ascribed to study drugs must resolve to baseline or ≤ grade 1, with the exception of alopecia; or ≤ grade 2 for pain in order for re-treatment to continue.

3.2.2 Hematologic Toxicity:

Given that hematologic toxicity is one of the major toxicities that may be experienced, all patients should have complete blood count measured and recorded weekly during the first 3 cycles and as needed, thereafter. However, if the ANC is ≤ 0.5 x 10^9/L or platelets are ≤ 25.0 x 10^9/L, CBC with differential must be redrawn more frequently, at least two times per week, until resolved.

Dose changes for satraplatin will be made based only on changes in the neutrophil and platelet counts. Satraplatin will be discontinued if neutropenia (≤ 0.5 x 10^9/L) lasting ≥ 5 days or thrombocytopenia (≤ 25 x 10^9/L) lasting ≥ 5 days despite dose reduction to 40mg/m2/d occurs, or if there is retreatment delay of > 8 weeks from Day 1 of prior cycle, due to study drug-related hematologic toxicities.
No growth factor support will be given prophylactically prior to starting satraplatin.

3.2.3 Hematologic toxicity Dose adjustments and reductions

Variable	Finding		Dose modification
	Platelets	ANC	

Variable	Finding		Dose modification
	Platelets	ANC	
Hematologic toxicity (based on previous cycle nadir*)	$\leq 25.0 \times 10^9$/L	$\leq 0.5 \times 10^9$/L	Decrease by 20mg/m^2 dose
Delayed recovery for Retreatment due to hematologic toxicity**	Less than or equal to 6 weeks		No change in dose level
	Between 6 and 8 weeks		Decrease by 20mg/m^2 dose
	More than 8 weeks		Off-study
Neutropenic fever			Decrease by 20mg/m^2 dose***

*Complete blood counts must be available on a weekly basis in the previous course
**Time from Day 1 of prior cycle.
***Growth factor support may be given for subsequent cycles as clinically indicated

3.2.4 Retreatment guidelines:

If satraplatin dosing is interrupted during a treatment cycle, it may be restarted as long as the planned 5 days of dosing occurs within an 8-day period (maximum interruption=3 days).
If there is more than a 3 consecutive day delay, no further doses should be given in the cycle.
The patient will be allowed to begin the next cycle a minimum of 35 days after the first day of the previous cycle if the criteria for re-treatment are met.

Patients may be retreated every 35 days if the following criteria are met:
-Hematologic toxicity-Absolute neutrophil count is $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L
-Non-hematologic toxicity ascribed to study drugs must resolve to baseline or $\leq$ grade 1, with the exception of alopecia; or $\leq$ grade 2 for pain in order for re-treatment to continue.

Laboratory tests may be performed up to 48 hours prior to the scheduled study visit and if the retreatment criteria are met, the patient may be retreated. If the re-treatment criteria are not met, the patient may not be retreated until they are met. <u>If therapy has to be held for more than 8 weeks from D1 of prior cycle, or > 3 weeks from the scheduled treatment, then the patient will be taken off-treatment.</u>

With the approval of the Principal Investigator, patients may be evaluated in offices of other Associate Investigator's (listed in the protocol) every other cycle starting with pre cycle 4. Study medications will continue to be dispensed by the NIH pharmacy. Restaging scans will be performed at NIH

3.2.5 Dose Modification for Prednisone:

Prednisone dose may be reduced to 5 mg once daily for $\geq$ grade 3 hyperglycemia or other toxicity attributed to prednisone. The dose may not be re-escalated following dose reduction.

Prednisone will be discontinued if untoward and unmanageable toxicity occurs (i.e., GI ulceration, symptomatic hyperglycemia unresponsive to medical therapy) despite dose reduction

to 5 mg per day. If prednisone is discontinued in the absence of disease progression, the patient will continue on satraplatin alone.

4 Correlative studies

4.1 Tissue analysis

Given the nature of this pharmacologic intervention, characterization of the actual biological manipulation will be helpful in understanding the biological effects seen following administration of satraplatin. Tissue samples may be analyzed to achieve this goal. In the recently published International Adjuvant Lung Cancer Trial (IALT) Bio Trial, immunohistochemical analysis to determine the expression of the excision repair cross-complementation group 1 (ERCC1) protein in operative specimens of non-small-cell lung cancer was performed and a benefit from cisplatin-based adjuvant chemotherapy was associated with the absence of ERCC1 (test for interaction, P=0.009).[44] When available samples obtained from selected prostate cancer patients may be utilized for ERCC1 staining using a commercially available mouse monoclonal antibody to human ERCC1 (clone 8F1, Neomarkers). Pharmacokinetic analysis will provide insight into dosing efficacy as it relates to both biological activity and clinical response.

Correlative laboratory studies for this trial will be conducted in the Clinical Pharmacology Section of Dr. William D. Figg at the NCI. All patients will have leukocyte collection to evaluate for ERCC1 expression. Patients with accessible disease may have tumor biopsies before and during treatment for ERCC1 protein analysis if feasible.

4.1.1 Accessible tumor biopsy

Biopsies of accessible tumors will be optional, and obtained prior to initiation of therapy and prior to starting cycle 2 as described. Patients should avoid the use of aspirin or non-steroidal anti-inflammatory drugs for 1 week prior to biopsy to ensure safety. Accessible tumors will be defined as those masses which can be safely accessed by a core needle biopsy while posing minimal risk to the patient. These lesions may be cutaneous or palpable or demonstrable under CT or ultrasound guidance. Determination of accessibility and safety will be made jointly by an investigator and a staff member from Special Procedures. Accessible tumors will be defined as those masses which can be safely accessed by a core needle biopsy under CT or ultrasound guidance or while posing minimal risk to the patient. Gareth Peters or Kathy Compton (10/5A09, 301-402-3622, 102-11964) should be contacted to arrange for sample collection. Biopsies are optional and will be limited to those that are easily accessible and involve minimal risk. The procurement of tissue samples will be discussed with patients at enrollment in the protocol. Biopsies will be obtained prior to initiating Satraplatin and prednisone (0 months), and after cycle 1. Participation in the phase II study is in no way contingent on consent to biopsy. If tissue is obtained from biopsies, the expression of ERCC1 will be assessed via immunohistochemical staining using commercially available antibodies. The tissue expression of ERCC1 will be correlated with patient's response to satraplatin.

4.2 Leukocyte analysis

In addition to the optional direct tumor biopsy, DNA will be isolated from whole blood for genotyping analysis as described in section 4.3 and collection as described in 4.3.2. Approximately 10 mL of blood will be drawn using a 10mL EDTA tube for DNA extraction.

The DNA will be stored at -80°C until the time of analysis. Approximately 8 mL of blood will be drawn using a 8mL CPT Sodium Citrate tube to isolate leukocytes to be lysed for genotyping analysis as described in section 4.3.2.1. The blood will be centrifuged and the buffy coat layer of white blood cells will be removed, washed and pelleted by centrifugation. The pellet will be frozen for future DNA extraction.

4.3 Genotyping analysis:

Genotyping will be done only on these genes and variants listed in this section:

Polymerase-chain reaction (PCR) followed by either restriction fragment length polymorphism (RFLP) or direct sequencing will be used to genotype the SNPs of ERCC1 Asn118Asn (C>T, rs11615), 8092C>A (3' UTR, rs3212986). Genotyping will not be limited to ERCC1 but may include the following: a) XRCC1 Arg194Trp (C>T, rs1799782), Arg399Gln (G>A, rs25489), and b) PARP1 Val762Ala (T>C, rs1136410).

We have excluded genotyping for XPD to avoid the possible clinical implications for carriers including transmission to offspring, childbearing and in the case of two mutant alleles of germline mutations in Xeroderma pigmentosum group D (XPD).

4.3.1 Patient Population and Scope of Studies

All study participants will have to provide a blood sample for genotyping of ERCC1 and other gene polymorphisms. The scope of the informed consent will also allow for the analysis of additional genes on a study specific basis.

4.3.2 Blood sample collection

Dr. William D Figg's laboratory, NCI is the designated laboratory, (POC, Mr. Gareth Peters, 10/5A09, or Ms. Kathy Compton, 301-402-3622, 102-11964).

4.3.2.1 Blood collection tubes

Prior to Day 1 of Cycle 1(may be collected at anytime during study if unavailable prior to start of therapy).

- **DNA** - Collect blood in 9 or 10 mL polypropylene tube containing the anticoagulant EDTA
  - SARSTEDT Monovette® EDTA KE (9 mL), Part # 02.1333.001 **or**
  - Becton-Dickinson Vacutainer™ K2E (10 mL), Part # 367525 **or**
  - Greiner Bio-One Vacuette® K3E EDTA K3 (9 mL), Part 455036
- Blood tubes must be gently inverted several times after collection to ensure thorough mixing of EDTA with the sample to prevent clotting.
- **Glass tubes MUST NOT be used** as they may break during transport and freeze-thaw cycles.
- **Heparin MUST NOT be used as an** anticoagulant as it may interfere with downstream genotyping methodology.
- **Buffy Coat** - Collect blood in a 8 mL polypropylene tube containing the anticoagulate sodium citrate

- Becton-Dickinson Vacutainer® CPT™ Cell Preparation Tube with Sodium Citrate, Part # 362761

- Blood tubes must be gently inverted 8-10 times after collection to ensure thorough mixing of sodium citrate with the blood.
- Blood tubes must be stored upright at room temperature until centrifugation.

4.3.2.2 Labeling, Storage, and Tracking

All samples sent to the Clinical Pharmacology Program (CPP) will be barcoded, with data entered and stored in the Patient Sample Data Management System (PSDMS) utilized by the CPP. This is a secure program, with access to the PSDM System limited to defined CPP personnel, who are issued individual user accounts. Installation of PSDMS is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All CPP personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

PSDMS creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without PSDMS access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

4.4 Protocol Completion/Sample Destruction

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the CPP and offsite at NCI Frederick Central Repository Services (Fisher Bioservices) in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in the PSDM System. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the CPP. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e. broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

5 Protocol Evaluation

5.1 BASELINE EVALUATION

- All patients who are deemed eligible and who sign an informed consent will be enrolled in this trial.
- A complete history and physical examination, including ECOG performance status (see Appendix A), will be done within 16 days of enrollment.

5.2 Laboratory Studies (see also Appendix C – Study Calendar)

- Serum PSA
- CBC with differential
- Serum chemistries (Na^+, K^+, Cl^-, CO_2, glucose, BUN, creatinine, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT, AST, total bilirubin, glucose, total protein, LDH)
- -Serum testosterone level

5.3 IMAGING SUTIDES

Non-invasive imaging has become a standard tool in the clinic to monitor primary and metastatic solid tumors. CT scan and bone scan will be performed on all patients at study entry and after every 2 cycles to assess clinical response to satraplatin and prednisone. However, CT scan will only be obtained if baseline CT shows positive disease.

6 Concurrent Therapies

Concurrent hormonal therapy with GnRH agonists to achieve testosterone suppression will be allowed. Concurrent anticancer treatment with chemotherapy, radiation therapy, major surgical procedures for prostate cancer, and nonprotocol-related immunotherapy will not be permitted. No growth factor support will be given prophylactically prior to starting satraplatin.

Patients who require hematopoietic growth factor support (e.g. epogen, darbepoetin), NSAIDs and other maintenance medications prior to study entry will be allowed to continue their supportive therapies. Filgrastim and sargramostim or other bone marrow stimulants are permitted when clinically indicated only after the first cycle.

Premedications will be used with the initiation of therapy following Clinical Center Anti-emetic guidelines and administered 30 – 60 minutes prior to study therapy. If granisetron is used, additional anti-emetics must be taken 8 hours after granisetron dose. Other anti-emetics, take as prescribed.

6.1 Nausea

Should patients develop persistent nausea, they will be given appropriate antiemetic therapy following clinical center guidelines. If this agent proves ineffective, the PI may use another antiemetic regimen (i.e. ondansetron, tropisetron or dolasetron). The type and period of all anitemetic therapy as well as any other concomitant medication administered will be recorded in the case report forms (CRF).

6.2 Diarrhea

Patients can be given loperamide for diarrhea

6.3 Analgesics for pain

Patients may use any analgesic for the treatment of pain, including narcotic and non-narcotic agents.

6.4 Concurrent use of bisphosphonates will be allowed

7 Criteria for Removal from protocol Therapy and Off Study Criteria

7.1 Criteria for Removal from Protocol Therapy

- Clinical progression of disease, appearance of one or more new lesions and/or unequivocal progression of existing lesions.
- Clear radiographic progression of disease by RECIST Criteria version 1.0
- Grade 3 or greater toxicity attributed to treatment, as defined in section 3.3 that does not resolve to grade 1, or pre-treatment baseline, within 3 weeks from next scheduled cycle.
- Neutropenia ($\leq 0.5 \times 10^9$/L) or thrombocytopenia ($\leq 25 \times 10^9$/L) that occurs despite dose reduction to 40mg/m2/d, or if there is retreatment delay of > 8 weeks from Day 1 of previous cycle
- Grade 4 vomiting or diarrhea that cannot be controlled by medical treatment and that occurs after one dose reduction will warrant discontinuation of satraplatin.
- Intolerable or limiting toxicity while on dose reduction of 40 mg/m^2.
- Intercurrent illness or medical circumstances. If at any time the constraints of this protocol are detrimental to the patient's health, the patient may be removed from protocol therapy and reasons for withdrawal will be documented.
- Patient requests to be taken off treatment. Reasons for withdrawal will be documented.
- Noncompliance with protocol guidelines (patient removed at discretion of Principal Investigator).
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Subject death.
- Patients who meet criteria for PSA progression may continue on treatment unless they meet the above criteria.

7.2 Post Treatment Evaluation

Once the patient is no longer receiving treatment (as per section 3.9), he may receive follow-up calls to monitor his well-being and progress. For patients who are taken off treatment due to treatment toxicities, a follow up evaluation will be conducted within a month and if subject will be taken off study. The phone calls will likely be annual though no specific guidelines shall be set.

7.3 Off Study Criteria:

The patient will be considered off study upon either patient's death or patient's decision to no longer participate in the study or post treatment follow-up.

7.3.1 Off-Study Procedure:

Authorized staff must notify Central Registration Office (CRO) when a patient is taken off-study. An off-study form from the web site (http://intranet.cancer.gov/ccr/welcome.htm) main page must be completed and faxed to 301-480-0757.

8 Data Collection

8.1 Patient Records and Quality Assurance

Data will be collected according to GCP (Good Clinical Practice Guidelines). Complete medical records on each patient treated on the protocol, including primary documentation (e.g., laboratory reports, x-ray reports, scan reports, pathology reports, physician notes, etc.) will be maintained and confirm the following:

- The patient met each eligibility criterion.
- Signed informed consent was obtained prior to treatment. (An on-study confirmation of eligibility form will be filled out before entering the study.)
- Documentation of specific dates and times of all treatments, doses administered, and the reason for any dose modification.
- Toxicity was assessed according to protocol (see section 11).
- Response was assessed according to protocol (x-ray, scan, lab reports, dated notes on measurements, and clinical assessment, as appropriate).

Data will be entered in a secure electronic database, NCI C3D database. Completed eligibility checklists (developed by Central Registration Office, CRO), and blood sample flow sheets will also be stored. Copies of all expedited reports submitted to the IRB and IND Safety Reports will be kept in the regulatory binder. Complete records must be maintained on each patient, including the medical record with any supplementary information obtained from outside laboratories, radiology reports, or physician's records. These records will serve as the primary source material.

8.1.1 Drug Accountability

The unused satraplatin blister packs will be returned for drug accountability at each clinic visit. An oral study agent case report form will be used to document drug accountability for each patient on this study. Unused agent, which is not returned to the patient for the next dose cycle, will be disposed of according to the Procedure of Disposal of Returned Oral agents. The Investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form. See the CCR Standard Operating Procedure: *Conducting and Documenting Drug Accountability for Oral Investigational Agents that are Self Administered by Patients* (http://ccrintra.cancer.gov/clin_ops/policies/SOPCLIN1.pdf).Patients will use a diary to document daily drug intake and adverse events. (See Appendix B)

8.2 Evaluation of Disease

For the purposes of this study, patients should be re-evaluated for response every 2 cycles for the duration of the study.

8.2.1 Definitions

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) Committee[67]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

8.2.1.1 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

8.2.1.2 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

8.2.1.3 Target lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

8.2.1.4 Non-target lesions

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

8.2.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.
The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the

antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US). When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

8.3 Response Criteria

8.3.1 Evaluation of target lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the

treatment started

8.3.2 Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of "non-target" lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

8.3.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see section 11).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
Any	Any	Yes	PD

Note:

X Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.

X In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

8.3.4 Confirmatory Measurement/Duration of Response

8.3.4.1 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

8.3.4.2 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

8.3.5 Biochemical Response Criteria –PSA measurements (PSA Consensus Criteria) [68]

8.3.5.1 PSA Decline of ≥50%

A decline of PSA of at least 50% (confirmed by a second value at least 4 weeks after the first) with no other evidence of disease progression.

8.3.5.2 PSA Progression (all progression dates require to be confirmed by a second value after the first no sooner than 4 weeks after the initial measurement)

A 50% increase in PSA over nadir (confirmed by a second reading four weeks later) in patients whose PSA has fallen by at least 50%. PSA increase must be at least 5ng/ml.

8.3.5.3 A 25% increase in PSA over nadir (confirmed by a second reading) in patients whose PSA has not fallen by at least 50%. PSA increase must be at least 5ng/ml.

8.3.5.4 A 25% increase in PSA over baseline in patients whose PSA has not decreased. PSA increase must be at least 5ng/ml.

8.3.5.5 Time to PSA Progression

The time between the first day of treatment to the day of PSA progression as described in 8.2.5.2 the day of progression is defined as the first study day when the PSA level meets progression criteria (not the day of verification).

8.3.5.6 Patients may continue to receive satraplatin as long as they do not have clear evidence of radiographic or clinical progression.

8.4 Toxicity Criteria

This study will utilize the CTCAE version 3.0 for grading adverse events. A copy of the CTCAE version 3.0 is available at http://ctep.cancer.gov. All appropriate treatment areas will have access to a copy of the CTCAE version 3.0.

9 Statistical Analysis

The primary objective of this single arm study is to determine if the presence of a polymorphism which is associated with DNA damage repair may be associated with an impact on the progression free survival of patients with metastatic prostate cancer.

A total of 66 evaluable patients will be accrued to the study and the evaluation will take place based upon the following anticipated characteristics of the trial:

The particular polymorphism of interest, ERCC1, has a WT (CC) prevalence of 19% in Caucasians (n=108) and 77% in African Americans (n=127). (Unpublished data) Based upon an estimate that 15% of projected patients to be enrolled on the study will be African American, the overall percentage of patients expected to have the WT genotype is 28%, and thus 72% are expected to express other genotypes other than wild type (TT or CT). Other studies have suggested that the presence of the WT genotype is associated with potentially lower progression free survival probabilities and that having the other genotypes would convey a more favorable prognosis [69].

This trial will treat all enrolled patients with satraplatin 80 mg/m^2 dose on days 1-5 of every 35-day cycle plus Prednisone 5 mg twice daily every 35 days, based on the Phase III SPARC trial. Preliminary data from this trial with a similar population of prostate cancer patients treated with the same agent had a 39% 6 month progression-free survival when pain is not included in the determination of PFS. It is unknown whether the results in this trial will be the same, but it will be conservatively estimated that for all patients taken together, the 6 month progression free survival will be the same 39%. If the patients enrolled on the present trial are distributed in the approximately expected proportion of 72% with non-wild type genotypes and 28% wild type, it would be of interest to determine if a modest difference in the proportion of patients who have not progressed by 6 months can be detected on the basis of their genotype. As this is meant to be a pilot investigation, using a one-tailed 0.10 alpha level Fisher's exact test, with 20 patients enrolled who have the wild type and 46 who have other genotypes (approximately a 28:72 split), would provide 80% power to detect a difference between proportions of patients without

progression at 6 months of 20% vs. 50%.

Although the primary endpoint will be determined using a Fisher's exact test, Kaplan-Meier curves with a log-rank evaluation will also be performed, although this will be considered a secondary analysis.

The entire group of 66 patients will also be evaluated using a Kaplan-Meier curve to describe the progression free survival of the group as a whole, as a secondary evaluation as well.

Overall survival will also be determined to the extent possible for the group of 66 patients as a whole and also as a function of the genotype expression described; this will be considered a secondary evaluation.

The trial will be conducted using a single stage design. However, to protect against the unlikely possibility that the agent will be associated with overall progression free survival which is substantially below what is expected based on results from other trials, an early stopping rule will be implemented as follows. After 20 patients have been enrolled and 6 months have passed since the 20th patient has enrolled, the proportion of patients who have attained 6 months without progression will be determined. If this fraction is no greater than 3/20 (15% who have attained 6 month progression free survival), then the trial will cease enrolling further patients because a one-sided 90% upper confidence bound on 3/20 is 30.4%, which would only indicate at best a modest probability of marginal consistency with what would be expected as the overall outcome using this agent. We will also perform genotyping for ERCC1 after the 20th patient, this is to test whether we are achieving the true probability of ERCC1 wild type proportion of 20% as indicated in earlier studies (in Caucasians). If the true probability is as shown, the probability of having 0 or 1 subject with WT genotype is tabled:

True WT proportion	Probability of getting 0 or 1 with WT
0.2	7%
0.1	39%
0.05	74%

Thus, if only 0 or 1 patient out of the first 20 patients should have ERCC1 WT genotype, then this would be more consistent with a 0.05 rather than a 0.20 true rate of WT. If this turns out to be the case, then we would re-evaluate the procedure for enrolling subjects to try to increase the proportion of patients with ERCC1 WT and amend the protocol accordingly.

Toxicity of the agent will also be tabulated for all patients taken as a group, and potentially by type of polymorphism genotype expression in the event that this may have some association. The distributions of toxicity identified will be compared informally to data from the same agent in other trials.

This trial will also explore other biologic correlates, as outlined above using genotyping for other DNA repair gene polymorphisms, white blood cell collections, and tumor biopsy, whenever possible. Monthly PSA, CBC, and serum chemistries will be performed at baseline and monthly thereafter, with CT scans and bone scans to be performed at baseline and every 10 weeks of treatment until progression. The comparisons will be made without any correction for multiple comparisons because of the exploratory and secondary nature of the evaluations.

9.1 Sample Size/Accrual Rate

Based on previous efforts in recruiting patients with this disease onto trials at the NCI, it is anticipated that 30 patients per year may be able to enroll onto this protocol. Thus, it is expected that accrual to this trial can be completed in approximately 2.5 years if all 66 patients are to be enrolled.

9.2 Stratification Factors

There are no stratification factors

9.3 Analysis of Secondary Endpoints

Genotyping, PSA, and molecular endpoints will be evaluated on the protocol in all available enrolled patients. These will all be considered exploratory analyses, and will not have their statistical results adjusted for multiple comparisons. However, all interesting findings will be carefully interpreted as hypothesis generating.

10 HUMAN SUBJECTS PROTECTIONS

10.1 Rationale for subject selection

Subjects treated on this study, will be individuals with metastatic prostate cancer, which has recurred (or persisted) after appropriate standard treatment. Individuals of any race or ethnic group will be eligible for this study. Eligibility assessment will be based solely on the patient's medical status. Recruitment of patients onto this study, will be through standard CCR mechanisms. No special recruitment efforts will be conducted.

10.2 Participation of Children

Individuals under the age of 18 will not be eligible to participate in this study because they are unlikely to have prostate cancer, and because of unknown toxicities in pediatric patient.

10.3 Evaluation of benefits and risks/discomforts

The potential benefit to a patient that goes onto study, is a reduction in the bulk of their tumor and improvement in their bony lesions, which may or may not have favorable impact on symptoms and/or survival. Potential risks include the possible occurrence of any of a range of side effects that are listed in the Consent Document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis.

10.4 Risks to patients in relation to anticipated benefits

For patients with androgen-independent prostate cancer, median survival is in the range of 12-18 months. Potential risks include the possible occurrence of any of a range of side effects listed in section 8.

Risk of serial biopsies: All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent. If patients suffer any physical injury as a result of the biopsies, immediate medical treatment is available at the NIH's Clinical Center in Bethesda, Maryland. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

10.5 Consent process

Patients will meet with an associate or principal investigator on the trial in the Prostate Cancer Clinic, during the initial evaluation for this study. During that meeting, the investigator will inform patients of the purpose, alternatives, treatment plan, research objectives and follow-up of this trial. The investigator will then provide a copy of the IRB-approved informed consent document that is included in this protocol. The patient will be allowed to take as much time as he wishes, in deciding whether or not he wishes to participate. If a prolonged period of time expires during the decision making process (several weeks, as an example), it may be necessary to reassess the patient for protocol eligibility. The original signed consent goes to Medical Records; copy placed in research record.

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on the study.

11 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

11.1 DEFINITIONS

11.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted below.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug. AEs that are considered treatment related, expected, continuing, but not resolvable by 30 days after treatment completion (e.g., alopecia) will not be followed after the 30-day period.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

Lymphopenia, alkaline phosphatase and lactate dehydrogenase of any grade will not be captured as Adverse Events.

11.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

11.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.4 Serious

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.1.5 Disability

A substantial disruption of a person's ability to conduct normal life functions.

11.1.6 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

11.1.7 Protocol Deviation (NIH definition)

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB.

11.1.8 Protocol Violation (NIH definition)

Any change, divergence, or departure from the study procedures in an IRB-approved research protocol that has a major impact on the subject's rights, safety, or well-being and/or the completeness, accuracy or reliability of the study data.

11.1.9 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; AND
- Is related or possibly related to participation in the research; AND
- Places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

11.2 NCI-IRB REPORTING

11.2.1 NCI-IRB Expedited Reporting of Adverse Events, Unanticipated Problems, and Deaths

The Protocol PI will report to the NCI-IRB:

- All unexpected serious adverse events that are possibly, probably, or definitely related to the research
- All deaths, except deaths due to progressive disease
- All Protocol Violations or Deviations
- All Unanticipated Problems

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

11.2.2 NCI-IRB Requirements for PI Reporting of Adverse Events at Continuing Review

The protocol PI will report to the NCI-IRB:

1. All Grade 2 unexpected events that are possibly, probably or definitely related to the research;
2. All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
3. All Grade 5 events regardless of attribution;
4. All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

11.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that require a sponsor recommended change to the protocol or the consent form or in the opinion of the PI increases risks to study participants will need to be reported to the NCI IRB.

11.3 NCI GUIDANCE FOR REPORTING EXPEDITED ADVERSE EVENTS FOR MULTI-CENTER TRIALS

The site PI must immediately report to the coordinating center PI any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event within 48 hours of PI awareness of the event. The Site PI must also report any protocol deviations or violations to the coordinating center PI within 7 days of PI awareness. Participating centers must also submit the report to their IRB in accordance with their institutional policies.

11.4 IND SPONSOR REPORTING CRITERIA

An investigator must immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

Study endpoints that are serious adverse events (e.g. all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g. death from anaphylaxis). In that case, the investigator must immediately report the death to the sponsor.

11.5 FDA REPORTING CRITERIA

11.5.1 Safety Reports to the FDA (Refer to 21 CFR 312.32)

The Sponsor will notify FDA via phone, fax, or email of any unexpected fatal or life-threatening suspected adverse reactions as soon as possible but no later than 7 calendar days of initial receipt of the information. This will be followed with a written report within 15 days using the MedWatch Form 3500a.

The study Sponsor will notify FDA in writing of any suspected adverse reaction that is both serious and unexpected as soon as possible but no later than 15 calendar days after initial receipt of the information using the MedWatch Form 3500a. If FDA requests any additional data or information, the sponsor must submit it to the FDA as soon as possible, but no later than 15 calendars days after receiving the request.

The study Sponsor will also report expeditiously as above:

- any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
- clinical important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

11.5.2 FDA Annual Reports (Refer to 21 CFR 312.33)

The study Sponsor will submit a brief report annually of the progress of the trial within 60 days of the anniversary date that the IND went into effect as indicated in 21CFR 312.33, and any associated FDA correspondences regarding the IND annual report.

11.5.3 Expedited Adverse Event Reporting Criteria to the IND Manufacturer

The initial telephone/facsimile report should contain as much information as is available

concerning the event in order to permit Agennix Inc. to file a report, which satisfies regulatory requirements. Initial telephone report of SAE must be followed-up by a completed SAE report (signed by the investigator) faxed to the Clinical Operations office of Agennix Inc. or designee. The event should also be entered into the source documents and case report forms, as appropriate.

If only limited information is initially available, follow-up reports will be required. A completed SAE form report should follow the initial phone call or incomplete fax report within 5 working days for all SAEs.

When additional information is available, a follow-up SAE report form should be faxed to the Agennix, Inc, or designee.

Any adverse events that are initially 'non-serious' but become 'serious' shall be reportable according to the time of the most recent classification.

One serious adverse event report (SAER) form will be completed per serious adverse event (SAE). The SAE term should match with the term captured on the AE page of the CRF. In order to avoid vague, ambiguous, or colloquial expressions, the AE term should be recorded in standard medical terminology.

For all serious adverse events, the Principal Investigator or an Associate Investigator will be responsible for completing the SAE Report Form and will fax the SAE Form within 24 hours of their knowledge of the event to Agennix Inc.

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11.6 DATA AND SAFETY MONITORING PLAN

11.6.1 Principal Investigator/Research Team

The clinical research team will meet weekly when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations and violations will be immediately reported to the IRB using iRIS and if applicable to the Sponsor.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the

research staff.

11.6.2 Sponsor Monitoring Plan

This trial will be monitored by personnel employed by Harris Technical Services on contract to the NCI, NIH. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

At least 25% of enrolled patients' will be randomly selected and monitored at least quarterly, base on accrual rate. The patients selected will have 100% source document verification done. Additional monitoring activities will include: adherence to protocol specified study eligibility, treatment plans, data collection for safety and efficacy, reporting and time frames of adverse events to the NCI IRB and FDA, and informed consent requirements. Written reports will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

11.6.3 Safety Monitoring Committee (SMC)

This protocol will require oversight from the Safety Monitoring Committee (SMC). Initial review will occur as soon as possible after the annual NCI-IRB continuing review date. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC. For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period. Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

12 Collaborative Agreement

The agent Satraplatin, supplied by Aggenix, Inc. used in this protocol is provided to the NCI under a Collaborative Agreement (CTA) between the Pharmaceutical Company and the Center for Cancer Research.

13 PHARMACEUTICAL INFORMATION

13.1 Satraplatin (IND 101,655)

13.1.1 Source:

Satraplatin, an investigational agent, will be supplied by Agennix Incorporated, Inc

13.1.2 Chemical name and identification

Chemical Name: bis(acetato)amine dichloro cyclohexylamine platinum (IV), is a member of a novel class of platinum (IV) compounds
Other Names: JM-216
Classification: Platinum analogue; platinum (IV) compounds
Mechanism of Action: Like other platinum agents, satraplatin exerts its biological activity via reactive biotransformation products that bind to DNA causing the inhibition of DNA replication , cell cycle arrest, and induction of apoptosis. Satraplatin is absorbed when administered by the oral route. The lipophilic properties of these compounds, and hence their absorption, are largely determined by the nature of the axial acetate ligands. Unlike the square planar platinum (II) complexes, cisplatin and carboplatin, Satraplatin is an octahedral platinum (IV) compound.

Molecular Formula: $C_{10}H_{22}N_2Cl_2O_4Pt$
M.W.: Satraplatin molecular weight is 500.29.

13.1.3 How Supplied:

Satraplatin capsules are either packaged in a) thermoformed blister packages constructed of a highly moisture impermeable and light protective film (dark amber ACLAR) and a push-through aluminum foil backing or b) in a primary package of aluminum blister strips and a push-through aluminum foil backing .Satraplatin is supplied as 1x5 capsules in blister strips. There are two strengths of capsules, one with 10 mg dose and the other with 50 mg dose.

13.1.4 Storage:

Store at controlled room temperature (15ºC -30ºC) and should be protected from light. Studies carried out in the presence of high humidity showed no apparent degradation of study drug.

13.1.5 Stability:

The drug product (10 and 50 mg satraplatin capsules) is labeled for storage at room temp. (15-30 °C) when contained within the secondary packaging (carton, box etc.). When stored under these conditions, stability is good to at least 30 months. All clinical supplies are on a formal stability or reassay program. Use-dating is monitored closely and extended annually.

13.1.6 Route of Administration:

Oral.

13.1.7 Reported Adverse Events and Potential Risks:

Body as a whole:	fatigue or asthenia, chills, headache, pain in chest or back, arthralgia, extremity pain, sweating, myalgia, bone pain
Hematologic:	myelosuppression, more specifically neutropenia and thrombocytopenia
Lung:	cough increased, dyspnea
Gastrointestinal:	diarrhea, nausea, vomiting, stomatitis, dyspepsia, anorexia, constipation, elevated liver enzymes, abdominal pain/cramping, nausea, flatulence, dyspepsia
Hepatic:	increased bilirubin, ALT, AST, and alkaline phosphatase
Metabolic and Nutritional:	decreased weight
Renal:	nephrotoxicity
Neurologic:	neurotoxicity(paresthesia), ototoxicity(deafness,otalgia, disorder or tinnitus), dizziness, changes in taste preservation
Musculoskeletal:	arthralgia
Cardiovascular:	tachycardia,syncope, hypotension
Other:	voice changes, hemoptysis

13.1.8 Method of Administration: Satraplatin should be taken with at least 120 ml to 240 mL of clear liquids (4-8 fluid ounces) and should be given without food (no food for 2 hours before or 1 hour after dosing).

13.1.9 Potential Drug Interactions

Satraplatin, has been shown to non-specifically inhibit numerous CYP450 isoenzymes in vitro. The clinical significance of the inhibition of CYP450 enzymes by satraplatin is unknown. Based on these in vitro data, close monitoring is recommended for patients taking agents with narrow therapeutic indices and metabolized by the liver, such as warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporine, and digoxin, and that patients should be monitored closely for drug interactions or adverse reactions to concomitant medications. Investigators are cautioned to adjust concomitant medication dosages as appropriate.

13.1.10Availability

Satraplatin is manufactured/supplied by Agennix Incorporated.

13.1.11 Agent Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs received from Agennix Incorporated using the NCI Drug Accountability Record Form (DARF). Satraplatin, as an oral self-administered investigational agent, will be properly accounted for, handled, and disposed in accordance with CCR Policy # Clin-1 "Policy on Documenting, Handling and Disposing of Oral Investigational Agents that are Self-Administered by NCI CCR patients." The Standard Operating Procedure # Clin-1 "Standard Operating Procedure for Conducting and Documenting Drug Accountability for Oral Investigational Agents that are Self Administered by Patients at the CCR" identifies all activities associated with drug accountability for orally self administered investigational agents. Patients will be instructed to document on a study diary the daily intake of satraplatin and prednisone, including the time the dose is taken, and whether or not any doses are missed (Appendix B). They will bring the study diary and any unused drug to their clinic appointments. Clinic staff will (1) collect all "old" [i.e., empty bottle(s), partial bottle(s) or full bottle(s)] of study drug; (2) perform a capsule count and record the results on the approved CCR Pill Count Case Report Form which is to be maintained in the research record; (3) dispense the partial and full bottle(s) of satraplatin to the patient. Unused study drug is to be returned to the research nurse who will dispose of it according to the SOP.

Upon completion or termination of the study, all unused and/or partially used study drug must be returned to Agennix Incorporated., if not authorized to be destroyed at the site. All drug returns to Agennix Incorporated must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping container.

The study subject should return all unused and/or partially used study drug at the end of each dosing cycle. Study drug to be returned includes study drug returned by subjects unused and/or partially used as well as drug wasted (e.g., dropped, incorrect dose, drug dispensed but not given). If drug may be destroyed at the site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by Agennix Incorporated, procedures for proper disposal have been established according to applicable regulations and guidelines and institutional procedures, and appropriate records of the disposal have been documented

13.2 Prednisone

13.2.1 Chemical name and identification

Chemical Name: Prednisone (17α,21-dihydroxypregna-1,4-diene-3,11,20-trione) is commercially formulated as the acetate salt (prednisone 21-acetate).
Other Names:
Classification: Steroids
Mechanism of Action: Multiple mechanisms leading to anti-inflammatory and immune suppression outcomes
Molecular Formula: $C_{23}H_{28}O_6$
M.W.: Prednisone molecular weight is 400.5

13.2.2 How Supplied:

Prednisone is supplied as a tablet or suspension. We will use commercially available prednisone stock acquired by the NIH Clinical Center Pharmacy.

13.2.3 Storage:

Prednisone should be stored in original containers at room temperature and should be protected from light.

13.2.4 Stability:

Prednisone is stable up to 3 years.

13.2.5 Route of Administration:

Oral

13.2.6 Reported Adverse Events and Potential Risks:

Body as a whole:	fatigue,
Ophthalmic:	cataracts, papilledema
Hematologic:	eosinopenia, leucocytosis, lymphopenia, thrombocytopenia, anemia
Gastrointestinal:	peptic ulcers, pancreatitis, abdominal pain
Hepatic:	increased bilirubin, ALT, AST, GGT, LDH, and alkaline phosphatase
Metabolic and Nutritional:	hyperglycemia, hyperuricemia, hypercalcemia, adrenal suppression, Cushing's syndrome, porphyria, lipid abnormalities, hypokalemia,
Renal:	nephrotoxicity, proteinuria
Neurologic:	psychosis, schizophrenic psychosis, extrapyramidal effects, pseudotumor cerebri,
Cardiovascular:	unknown
Skin:	acne
Musculoskeletal:	osteonecrosis, osteoporosis, myopathy
Other:	Superinfections

13.2.7 Method of Administration: Prednisone should be taken with at least 120 ml to 250 mL of water and should be given without food. However, if patients develop GI distress, dosing schedule can be modified to be taken with food.

13.2.8 Availability

Prednisone will be obtained from commercial stock purchased by the NIH CC Pharmacy Department

13.2.9 Agent Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs using the NCI Drug Accountability Record Form (DARF). Prednisone, as an oral self-administered investigational agent, will be properly accounted for, handled, and disposed in accordance with CCR Policy # Clin-1 "Policy on Documenting, Handling and Disposing of Oral Investigational Agents that are Self-Administered by NCI CCR patients." The Standard Operating Procedure # Clin-1 "Standard Operating Procedure for Conducting and Documenting Drug Accountability for Oral Investigational Agents that are Self Administered by Patients at the CCR" identifies all activities associated with drug accountability for orally self administered investigational agents. Patients will be instructed to document on a study diary the daily intake of satraplatin and prednisone (Appendix C), including the time the dose is taken, and whether or not any doses are missed. They will bring the study diary and any unused drug to their clinic appointments. Clinic staff will (1) collect all "old" [i.e., empty bottle(s), partial bottle(s) or full bottle(s)] of study drug; (2) perform a capsule count and record the results in the electronic record, CRIS; (3) dispense the partial and full bottle(s) of prednisone to the patient. Unused study drug is to be returned to the research nurse who will dispose of it according to the SOP.

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15 PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

16 Appendix B: Patients' Pill Diary

Today's Date_____

Patient Name_____ Patient Study ID_____

Total dose of Satraplatin (in milligrams)_____

Cycle Number_____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle.

2. You will take____pills of 50mg Satraplatin pill and ___ pills of 10mg Satraplatin pill each day on Days 1-5. You must take the pills on an empty stomach, no food for two hours before, or one hour after Satraplatin. Anti-nausea pill must be taken 30-60 minutes before Satraplatin dose.

3. You will take 1 pill of Prednisone (5mg) in the morning and 1 pill of Prednisone (5mg) in the evening on Days 1-35. On days 1-5 when you're on Satraplatin, the AM dose of prednisone must be taken 2 hours before the Satraplatin.

4. Record the date, the number of pills you took, and when you took them.

5. Any symptoms or observations may be noted under the COMMENTS column.

6. Please bring your pill bottle and this form to your physician when you go for you next appointment.

17 APPENDIX C. Study Calendar

Schedules shown in the Study Calendar below are provided as an example and should be modified as appropriate (+/- 1-2 days to allow for clinic variations around federal holidays).

Procedure	***Screening/ Baseline***	***Every Cycle Days (1-5)***	***Every Cycle Days (1-35)***	***Every Cycle***	***Every 2 Cycles***
Medical History	X			X	
Physical Exam	X			X	
Informed Consent	X				
Vital Signs	X			X	
Height	X			X	
Weight	X			X	
Performance Status	X			X	
Demographics	X				
Concurrent Medications	X			X	
Tumor Biopsy ***(optional)***	X and C2D1				
Labs • *CBC with diff* • *Platelet count* • *PT and apt* • *Chemistry Panel*[a] • *PSA* • *Testosterone level*	X			X	
Correlative Research Studies[b]	X[b]				
Radiological Assessments • *CT Scan (chest, abdomen, pelvis)* • *Technetium*^{99} *Bone Scan*	X				X
Chest X-Ray	X				X
EKG	X				
Tumor Measurements	X				X
Adverse Events Evaluation	X			X	
SATRAPLATIN[c]		X			
PREDNISONE		X	X		

[a] Chemistry Panel includes: electrolytes, BUN, creatinine, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT, AST, total bilirubin, total protein, LDH, testosterone level

[b] If Correlative Research Study is missed prior to Day 1, may be drawn (one time blood draw) at any point throughout study.

[c] Dose as assigned: route/schedule

INSTITUTE: National Cancer Institute

STUDY NUMBER: 08-C-0074 PRINCIPAL INVESTIGATOR: William Dahut, MD

STUDY TITLE: A Phase II Study of Satraplatin and Prednisone in Metastatic Androgen Independent Prostate Cancer (AIPC)

Continuing Review Approved by the IRB on 2/14/11

Amendment Approved by the IRB on 5/18/11 (F) Date Posted to Web: 5/26/11

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

If you are signing for a minor child, "you" refers to "your child" throughout the consent document.

In an attempt to develop more effective treatments for cancer, we propose treating you with Satraplatin and prednisone. Satraplatin is an experimental drug which may soon be approved for prostate cancer. Prednisone has been approved for use in prostate cancer.

You should understand that this study involves research. Eligibility criteria are routinely used to assure that patients who enter experimental studies are medically appropriate candidates for this therapy and that they have the carefully defined medical condition as outlined by the study protocol. For your own well being, as well as to ensure that the results of this study can be useful to making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study. If new information is gained regarding your disease or related to the drug being studied, we may discuss that information with you.

Description of Research Study

This study involves your voluntary participation in a research protocol. The purpose of this research is to know whether the drug satraplatin may help treat your prostate cancer depending on the presence of specific genes. Satraplatin is currently being studied in prostate cancer patients and has been found to benefit them. This study is designed with the satraplatin being given along with another drug called prednisone, which is also being used for prostate cancer. Blood work will be done to determine if you possess a certain type of gene called ERCC1 or its variant genes, and to see if possession of these genes will help make the drug work better or not. A gene is a hereditary unit passed from parent to offspring. Genes are made up of pieces of DNA and most genes contain the information for making a specific protein that performs important functions in our body. Changes or variations in the DNA of our genes can change the function of the protein made by the gene. ERCC1 is a gene that helps repair damage brought about by the chemotherapy drug satraplatin. Blood work will be done to determine if you have any variants in your ERCC1 gene and to see whether any of the variants in the ERCC1 gene help make the drug work better or not. If you have an ERCC1 variant that repairs the damage done by the chemotherapy drug satraplatin, the drug may not work well for your prostate cancer because it will not be able to damage the cancer cells effectively. This study will try to determine whether this hypothesis is true or not.

There will be other genes that we will test for including XRCC1 and PARP1. However, these tests will be for study purposes only and will remain strictly confidential and results will not be disclosed to anyone.

The drug satraplatin is currently not FDA approved yet because more time is needed to determine possible survival benefits, but studies have been conducted using satraplatin in tumors like lung cancer, ovarian cancer and prostate cancer. Prednisone is a drug which is being used in combination with other drugs approved for prostate cancer.

Satraplatin (a type of chemotherapy) will be taken by mouth every day for five consecutive days out of every thirty-five days. The Satraplatin pills (the number of pills depend on your weight and height) must be taken in the morning for 5 straight days, with no food for 2 hours before or 1 hour after the dose. Every 35 days constitute a "cycle". In addition, we will ask you to take a pill to prevent nausea and vomiting 1 hour before as well as taking the prednisone pill two times a day (morning and evening) every day while you're on-study.

The blood test to look for the variants in your ERCC1 gene will be done and analysis of the results will be made after the first 20 patients get enrolled. For the first 3 cycles of every 35 days each, you will need to get blood drawn weekly either here at NIH or at your local doctor's office to see whether your blood counts don't get too low since your dose of Satraplatin may need to be adjusted at your next cycle.

We will repeat some of the studies (e.g., bone scan and/or CT scan) to determine if your cancer has responded approximately every 70 days. If there are no severe signs of toxicity or if your cancer has not progressed we will continue to give you satraplatin and prednisone. Your experimental treatment is designed to be as an outpatient (with the exception of the first and fifth dose of the first cycle where you may spend several nights in the Clinical Center Hospital). This investigational therapy could last greater than 6 months, depending on whether you are gaining benefit from this experimental treatment and not experiencing side effects.

It is possible that some of the prostate cancer cells in your body may still grow if exposed to the male hormone testosterone. Thus your testosterone must be suppressed either surgically (removal of the testicles) or medically with an injection (shot) with a luteinizing hormone-release hormone (LHRH) agonist (leuprolide or goserelin). LHRH agonists are drugs that reduce the amount of the male hormone testosterone.

Your doctors have told you that you have advanced prostate cancer that is not responding to hormonal therapy. Your doctors have told you that although "standard" treatment could be administered to you, there is no known curative option for your cancer. For this reason, we are offering you experimental treatment on this research study. Although we hope

that this experimental therapy may benefit you and that your disease will not progress, there is no guarantee that your tumor will respond. Benefit cannot be promised, nor can the chance of benefit be accurately predicted. Likewise, we cannot promise you that these drugs will not cause some side effects.

Before receiving any form of treatment, you will be evaluated in the outpatient clinic to see if you are eligible for this experimental therapy. You are being offered this therapy because you have cancer of the prostate, which has been treated with hormone therapy or at least one type of chemotherapy, but now shows a rising PSA. X-rays, scans, or other tests must show evidence for spread of the cancer (metastases).

Your participation in this research project will be for a period of at least 3 to 6 months, although this period may be shorter or longer depending on the response of your tumor or if you experience serious side effects.

The procedure for this project involves an initial evaluation in the outpatient clinic to see if you qualify for this study. This evaluation phase may last from several days to several weeks. Additional blood tests will check to see if your liver, kidneys, and other organs are working well enough to be safe to start the treatment. Altogether these initial tests will require about 35 cc (2 tablespoonfuls) of blood. Finally, before starting treatment, bone scan, x-rays or other ways of taking pictures of your internal organs and measuring your tumor with computerized tomography (CT scans) and/or magnetic resonance imaging (MRI scans) will be obtained, as well as evaluation of your heart with the electrocardiogram tracing (EKG).

The treatment plan is outlined above. If you do not experience bad side effects (see below) and if your tumor does not grow at the time of the first 2 cycles, the cycles will be repeated every five weeks. If you experience unacceptable side effects (toxicities) at any time in the study, you will not receive additional treatments on this study. You will have your scans and x-rays repeated approximately every 70 days while on study.

A total of up to 66 patients/human volunteers are expected to participate in this project.

Risk or Discomforts of Participation

We are asking you to participate in this study. Both of these drugs have been given to humans and thus we have a good idea of the potential side effects you may develop. The combination of both satraplatin plus prednisone has been administered together, thus, we can predict the side effects that you may experience based on a recently concluded trial that also used the same combination. You will be monitored closely while you are receiving this experimental treatment for any signs that might signal the earliest stage of toxicity so that appropriate intervention can be done.

It is extremely important that you notify us before starting to take any new medications that your local doctors may have prescribed, or that you may purchase over the counter at a drug store (cold medication and antacids for your stomach). Satraplatin can have an interaction with several other drugs. Thus, you should notify us if you start any new treatments.

The more common side effects that have been associated with satraplatin include:

- decreased platelet count, decreased red blood cell count, decreased white blood cell count (neutropenia) – occurring in about 21%
- mild bruising may accompany the decreased platelet counts
- nausea, vomiting, diarrhea, constipation is also common, occurring at about 58% of patients

Other less common complications include: abdominal pain, flatulence, numbness or tingling, diarrhea, elevated liver enzymes, fatigue, headache, dizziness, myalgia, fever, chills, fast heart beat, syncope (fainting), low blood pressure,

changes in hearing, kidney dysfunction, pain in the arms, chest, back or legs, blood clot, shortness of breath, and cough.

The side effects that have been associated with prednisone include:

- gastric hyperacidity(increased stomach acid), increased appetite, insomnia or nervousness occurring in > 10% of patients
- hyperglycemia (high blood sugar level), fluid retention, mood swings, dizziness, headaches, muscle weakness, osteoporosis (bone thinning), and cataracts with long-term use, occurring in about 1% - 10% of patients
- Hypertension occurring in < 1% of patients

The side effects that have been associated with the pill to prevent nausea or vomiting (like granisetron for prevention of nausea or vomiting) include:

- Headache (occurring around 9% - 21% of patients)
- Fatigue or weakness (occurring around 5% - 18% of patients)
- Constipation (occurring around 3% - 18% of patients)

Less common side-effects include: hypertension, pain, dizziness,insomnia, somnolence, anxiety, agitation or stimulation, rash, diarrhea, abdominal pain, elevated liver enzymes, decreased urination, cough, infection which occurs in 1% to 10% of patients, and rare (<1%) but important or life-threatening reactions include: allergy to the drug, increased or abnormal heart beat, or syncope (fainting).

We will also ask you to allow us to perform a tumor biopsy, whenever feasible, to look at the level of expression of this gene ERCC1 in your tumor, and correlate that with your response to the chemotherapy drug satraplatin. We will coordinate with the radiologists in Special Procedures department to look at your CT Scans to see if the tumor can be biopsied. A numbing medication similar to lidocaine is used prior to this procedure. The side effects include, but are not limited to pain, infection and the risk of bleeding. A separate consent form will be provided to you to describe the tumor biopsy procedure in more detail as well as any additional side effects should you consent to the procedure. This procedure is optional and consenting to the study is not contingent upon your consent to the procedure.

Potential Benefit

This is a phase II study, which means we are trying to determine whether the combination of the drug satraplatin and prednisone will be beneficial to treat your prostate cancer if you possess the variant ERCC1 gene or not.

Benefit cannot be promised, nor can the chance of benefit be accurately predicted. It is possible that you may experience some, all, or none of the side effects described above. It is also possible that either the satraplatin or the prednisone may produce some unanticipated side effects. For that reason, you will be monitored closely while you are receiving this experimental treatment for any signs that might signal the earliest stage of toxicity so that appropriate intervention can be done.

Alternative Treatments

The standard treatment for patients with metastatic prostate cancer is hormonal therapy. However, when patients' cancer continues to progress despite hormonal therapy (AIPC), there is no clear standard of therapy. Patients may be treated with radiotherapy, investigational agents, chemotherapy or sometimes observed. Ketoconazole and hydrocortisone is sometimes used alone in this setting. The role of chemotherapy in patients with AIPC has historically been questioned due to the lack of efficacy in the agents used. However, newer agents and combinations are being investigated. The combination of mitoxantrone and prednisone has shown palliative benefits. Docetaxel and prednisone has shown improved overall survival benefit, as well as docetaxel and estramustine. Satraplatin has also been used with prednisone and has improved progression-free survival, as presented in a major medical meeting.

Other options include palliate care, which includes:

- Getting no treatment.
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Cost and Reimbursement

If you choose to participate in this study, your medical care and the costs of the laboratory and radiographic studies done at the Clinical Center, National Institutes of Health will be at no charge to you. The NIH cannot reimburse you for the costs of medical care delivered outside the NIH, even if you are seeking medical attention as a result of side effects of treatment given on this study. Similarly, you cannot be reimbursed if you choose to have diagnostic radiographic tests (such as chest x-rays or CT scans) performed locally (outside of the NIH), even if they are done for the purposes of this study.

Communication

The NCI physicians involved in your care are available to answer all of your questions concerning this protocol. If you have any concerns or questions, you may contact Dr. William Dahut, the Principal Investigator at (301) 435-8183, or Associate Investigators Dr. James Gulley at (301) 435-2956, Dr. Philip Arlen at (301) 496-0629 or the research nurses, Lea Latham at (301) 402-9137, Marcia Mulquin at (301) 435-5613 or David Draper at (301) 435-5614. If you have any complications when you are not in the Clinical Center (e.g., at home or in a local hotel), you may call the page operator at (301) 496-1211 and ask for either the NCI Medical Oncology Branch physician on call or the NIH Patients' Rights Representative who will be available to answer questions concerning your involvement in this study or your rights as a research subject. She is not directly associated with this study and can be contacted at (301) 496-2626.

Research Subjects' Rights

You will be told if no benefit occurs to you as a result of taking part in this treatment program and the program will be stopped.

You will receive a copy of this informed consent for your own records. In addition, a copy of the informed consent is on file with the Medicine Branch of the National Cancer Institute and a copy will be made available to you whenever you want to see it. Your records will be kept confidential, with the exception that the FDA, the drug company that manufactures the appropriate study drugs may have access to your medical record, as well as the staff of the National Cancer Institute, and representatives of GPC Biotech, Inc. may inspect and study your medical records.

Your participation in this study is entirely voluntary, and you may refuse to participate, or withdraw from this protocol at any time and receive care from your referring physician.

Your participation in this study may be ended by the Principal Investigator or an Associate Investigator without your consent if they feel termination is medically indicated.

Upon completing this study, you may be given the choice of taking part in other research protocols that may be appropriate for you. Otherwise, you will be returned to the care of your referring physician. It is important to stress that your participation in this study does not constitute a promise of long term care at the NIH Clinical Center. If there is no research study that can help you, you will be returned to the care of your private doctor. If you do take part in this study, you may be unable to take part in certain other research protocols because these protocols may not allow patients who have been on certain drugs to enter. You may decide now not to receive treatment in this protocol, or you may choose at any time to stop the drug and withdraw from the protocol. In either case, you would be returned to the care of your referring physician.

Your signature on this consent indicates that you agree to participate in this medical research study under the direction of the principal investigator as listed above. In addition to your signature, please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. If you have questions, please talk to your physician or nurse, or call the NCI's Cancer Information Service at 1-800-422-6237 (1-800-4-CANCER)

My tissue (specimen) may be kept for use in research to learn about, prevent, or treat cancer:

Yes_____ No_____ Initials_____

My tissue (specimen) may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes_____ No_____ Initials_____

OTHER PERTINENT INFORMATION

1. **Confidentiality.** When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

   The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. **Policy Regarding Research-Related Injuries.** The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. **Payments.** The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. **Problems or Questions**. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact Dr. William Dahut, the Principal Investigator at (301) 435-8183, or Associate Investigators Dr. James Gulley at (301) 435-2956, or Dr. Philip Arlen at (301) 496-0629. You may also call the Clinical Center Patient Representative at 301-496-2626.

5. **Consent Document.** Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative Date

Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian Date

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian Date Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM FEBRUARY 14, 2011 THROUGH FEBRUARY 13, 2012.

Signature of Investigator Date

Print Name

Signature of Witness Date

Print Name