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SWOG

ABIRATERONE ACETATE TREATMENT FOR PROSTATE CANCER PATIENTS WITH A PSA OF MORE THAN FOUR FOLLOWING INITIAL ANDROGEN DEPRIVATION THERAPY
PHASE II

NCT01309672

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SWOG-held IND Agents:
Abiraterone Acetate (NSC-748121) (IND-111552)

IND-Exempt Agents:
Prednisone (NSC-10023)

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1.0 OBJECTIVES

1.1 Primary Objective

To assess the rate of achieving a PSA of ≤ 0.2 ng/ml with abiraterone acetate therapy in men with metastatic prostate cancer with a suboptimal response to androgen deprivation therapy (ADT). The undetectable level of PSA will be confirmed by a second measurement with a PSA ≤ 0.2 ng/ml at least 4 weeks later, without any evidence for progression. Subjects who fail to reach and confirm a PSA of ≤ 0.2 ng/ml by 12 months will be considered a non-responder with regard to the primary endpoint.

1.2 Secondary Objectives

a. To assess the overall survival and objective progression-free survival in this group of patients.

b. To assess PSA partial response.

c. To evaluate the qualitative and quantitative toxicity of abiraterone acetate.

2.0 BACKGROUND

The cornerstone of medical management of metastatic prostate cancer is androgen deprivation therapy (ADT). The clinical utility of ADT was championed by Charles Huggins who reported the dramatic effect of ADT in prostate cancer in the 1940's, in work that led to the Nobel Prize in 1966. *(1)* ADT was initially achieved through bilateral surgical castration although most men in the current era prefer ADT medically via gonadotropin releasing hormone agonist therapy (GNRH).

Using data from a SWOG Phase III trial examining the efficacy of continuous versus intermittent ADT in men with metastatic disease in **SWOG-9346**, Hussain and colleagues reported on the prognostic value of the PSA nadir after the initial hormone induction portion of the trial. At the end of the 7 month induction period, those patients with a PSA of ≤ 0.2 ng/ml had a median survival of 75 months, those with a PSA of 0.2 - 4 ng/ml a survival of 44 months and for those patients with a PSA of > 4.0 ng/ml, the median survival was only 13 months. *(2)* This report included both non-responders and partial responders. An additional analysis found that subjects who failed to achieve a PSA of < 4 ng/ml and did not exhibit a rising PSA at 7 months had a median overall survival of approximately 21 months from this assessment timepoint.

Abiraterone Acetate: Rationale and Background

Developing data suggests that the low levels of androgen that persist despite ADT may play an important role in the development of castrate resistant prostate cancer (CRPC). In both the testis and the adrenal glands, cytochrome P 17 (CYP17) catalyzes two key reactions involving the enzymes 17α-hydroxylase and C17,20-lyase, converting steroid precursors into androgens. By this mechanism, low levels of circulating testosterone persist despite surgical orchiectomy or GNRH agonist/antagonist therapy. In castrate men, up to 10% of the normal levels of testosterone may be observed by this mechanism. *(3)*

Alterations and mutations in prostate cancer cells have also been identified as a cause of the development of CRPC. Increased gene expression of CYP17, the enzyme targeted by abiraterone acetate, has been correlated with higher stage and Gleason grade in prostate cancer, suggesting the possibility of autonomous steroidogenesis in prostate cancer cells. *(4)* Gene expression analysis of androgen-sensitive prostate cancer and CRPC reveal increased expression of genes capable of converting adrenal androgens into testosterone. *(5)* Surprisingly, recent investigations have observed similar levels of testosterone in recurrent prostate cancer

tissue as compared to androgen-stimulated benign prostate tissue. *(6)* It is also known that in response to the low levels of testosterone after ADT, the androgen receptor (AR) has increased expression with genetic amplification, potentially allowing AR signaling even with low levels of testosterone. *(7,8,9)* Taken together, these data argue that the lowest possible level of androgen should be the therapeutic objective in men with CRPC.

Abiraterone acetate and its metabolite abiraterone are selective steroidal inhibitors of CYP17 and its associated enzymatic activity. *(10)* The clinical importance of the low androgen levels observed despite GNRH agonist therapy is clear from the regular use and benefit of secondary hormonal therapies. For example, ketoconazole does have activity in prostate cancer patients with PSA progression despite ADT. *(11,12,13,14)* In this setting, ketoconazole acts as a non-specific inhibitor of several adrenal enzymes including 17α hydroxylase/C17,20-lyase, with its non-specific mechanism requiring the use of glucocorticoids to prevent adrenal insufficiency. One analysis correlated the level of adrenal androgens to PSA responses, finding that patients with unmeasurable or very low adrenal androgens were less likely to respond to ketoconazole than those with higher levels. *(15)* In contrast to the non-specific effects of ketoconazole, abiraterone acetate is a targeted CYP 17 inhibitor, with the potential to minimize the adverse events seen with ketoconazole.

Over 420 subjects have been exposed to abiraterone acetate in Cougar-sponsored Phase I and II open label studies in the United States and the United Kingdom. In the two Phase III studies, COU-AA-301 and COU-AA-302, subjects have been exposed to abiraterone acetate and placebo in a 2:1 ratio, and 1:1 ratio, respectively. *(16)* Overall, abiraterone acetate has been very well tolerated with no dose limiting toxicity observed in several trials treating patients with up to 2,000 mg daily. Some evidence of secondary mineralocorticoid excess (hypertension, hypokalemia and edema) has been observed in the initial studies; it is now recommended that abiraterone acetate be given with a low dose of glucocorticoid such as prednisone 5 mg po twice daily to abrogate these symptoms, while others have advocated the use of a mineralocorticoid receptor antagonist. *(17)* Based on the PK profile and the overall toxicity pattern, the recommended Phase II testing dose of abiraterone acetate is 1,000 mg daily and this regimen in combination with prednisone of 5 mg twice a day in the Phase III trials.

Abiraterone Acetate Efficacy Data

The initial human trials of abiraterone acetate were recently reported. *(18)* The main objective of these studies was to determine the effect of abiraterone acetate on testosterone levels in both normal and medically castrate men. In single-dose testing, 10 to 800 mg of abiraterone acetate was administered. A repeated-dose cohort of castrated men was also treated with abiraterone acetate of 500 or 800 mg by mouth on a daily basis. Overall, these studies showed that testosterone could be suppressed without any significant change in cortisol levels in both castrate and non-castrate men. In castrate men, a single 500 mg dose was able to suppress the testosterone to less than 0.14 nmol/L in four of six participants. Repeated treatment of non-castrate men with 800 mg daily of abiraterone acetate did achieve testosterone suppression to castrate levels, although this wasn't sustained likely due to compensatory luteinizing hormone (LH) hypersecretion.

Ryan et al. have reported on the use of abiraterone acetate in a Phase I trial of men with CRPC. *(19)* Dose escalation was performed with a daily dose range of 250 to 1,000 mg. Of 33 treated men, 18 (55%) achieved a PSA reduction of > 50% to constitute a PSA response. At the recommended Phase II testing dose of 1,000 mg daily, six (50%) of 12 patients experienced a PSA response. Prior ketoconazole was allowed; of the 19 patients previously treated with ketoconazole, 10 (53%) had a PSA response. These results show promising activity, regardless of previous treatment with ketoconazole, and suggest that despite an overlapping mechanism of action, abiraterone may be effective when ketoconazole is not. Danila, et al. have described the use of abiraterone acetate in men with CRPC who have failed docetaxel chemotherapy. *(20)* Thirty-eight patients were treated with a median baseline PSA of 86 ng/ml, 45% had previously received ketoconazole, 32% had one previous line of chemotherapy and 68% had two previous lines of chemotherapy. Thirty-five patients were evaluable at the time of this analysis; at three

months, 14 (40%) of 35 had a PSA response with a reduction of > 50% from their baseline value. There was no a clear difference in PSA responses based on prior exposure to ketoconazole.

To better determine the effect of abiraterone on castrate men with prostate cancer, Riggs et al. followed the testosterone levels in 12 men receiving abiraterone acetate. *(21)* Using liquid chromatography and tandem mass spectrometry detections, ultrasensitive assessments of testosterone were obtained. All men were being treated with GNRH agonists and had a mean testosterone of 3.86 ng/dl prior to starting abiraterone acetate. Ultrasensitive testosterone testing revealed that 11 of the 12 patients achieved testosterone levels of < 1 ng/dl over four weekly measurements, confirming the ability of abiraterone to quantitatively reduce testosterone in men already receiving GNRH agonist therapy.

Investigators at the Royal Marsden Hospital reported on 21 chemotherapy naïve men with CRPC who were treated with abiraterone acetate at doses of 250 to 2,000 mg daily. A PSA reduction of > 50% that was maintained for at least three months was observed in 12 (57%) of 21 patients. Of the eight patients with measurable disease, five (62%) achieved a confirmed partial response using RECIST criteria. In addition, eight of 11 patients who required analgesia at baseline for pain had a reduction or complete resolution of their pain with abiraterone acetate therapy. *(22)*

In summary, abiraterone acetate is a potent and specific inhibitor of testosterone production and represents a new generation of ADT. It has clear activity in men with CRPC as documented in several human trials. An analysis of the data from **SWOG-9346** indicates that prostate cancer patients who fail to achieve a stable PSA of less than or equal to 4 ng/ml have a poor prognosis. The use of abiraterone acetate in this high-risk patient population is rational and compelling. While the men eligible for the current study are not necessarily castrate resistant by the traditional definition, they are only partially responsive to ADT. Due to practical considerations, the eligibility criteria for the current study are modified slightly from the **SWOG-9346** criteria, since the goal of the current study is to determine the activity of abiraterone acetate in this population and generate data for larger, future trials. The early use of abiraterone acetate in these men may potentiate ADT, prolonging the progression-free survival and postponing the need for more toxic chemotherapy.

At the time of **S1014** activation, the results of COU-301 had been published. In a 2:1 ratio, 1,195 men with castration-resistant prostate cancer and previous docetaxel chemotherapy were treated with abiraterone acetate and prednisone versus placebo and prednisone. There was a statistically significant improvement in median overall survival (14.8 versus 10.9 months) favoring the abiraterone arm ($p<0.001$). There was also improvement in the time to PSA progression, progression-free survival and PSA response rate in the abiraterone acetate treatment arm. *(23)* Abiraterone acetate with prednisone was approved by the FDA in April 2011 for use in metastatic castration-resistant prostate cancer following docetaxel.

Inclusion of Minorities:

This study was designed to include minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

Ethnic Category	Females	Males	Total
Hispanic or Latino	0	4	4
Not Hispanic or Latino	0	34	34
Total Ethnic	0	38	38
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	1	1
Black or African American	0	7	7
Native Hawaiian or other Pacific Islander	0	0	0
White	0	30	30
Racial Category: Total of all Subjects	0	38	38

3.0 DRUG INFORMATION

Investigator's Brochure

For information regarding Investigator's Brochures, please refer to SWOG Policy 15.

For this study, abiraterone acetate is investigational and is being provided under an IND held by SWOG. For IND's filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

For this study, prednisone is commercially available; therefore, an Investigator Brochure is not applicable to this drug. Information about commercial drugs is publicly available in the Physician's Desk Reference (PDR), prescribing information and other resources.

3.1 Abiraterone Acetate (CB7630) (NSC #748121) (IND-111552)

a. PHARMACOLOGY

Abiraterone acetate is converted in vivo to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal and prostatic tumor tissues and is required for androgen biosynthesis. CYP17 catalyzes two sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives by 17α-hydroxylase activity and 2) the subsequent formation of

dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals.

b. PHARMACOKINETICS

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects and in patients with metastatic castrate resistant prostate cancer (CRPC). In vivo, abiraterone acetate is converted to abiraterone. In clinical studies, abiraterone acetate plasma concentrations were below detectable levels (< 0.2 ng/mL) in > 99% of the analyzed samples.

1. Absorption: Following oral administration of abiraterone acetate to patients with metastatic CRPC, the median time to reach maximum plasma abiraterone concentrations is 2 hours. Abiraterone accumulation is observed at steady-state, with a 2-fold higher exposure (steady-state AUC) compared to a single 1,000 mg dose of abiraterone acetate. At the dose of 1,000 mg daily in patients with metastatic CRPC, steady-state values (mean ± SD) of C_{max} were 226 ± 178 ng/mL and of AUC were 1173 ± 690 ng.hr/mL. No major deviation from dose proportionality was observed in the dose range of 250 mg to 1,000 mg.

   Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. Abiraterone C_{max} and $AUC_{0-\infty}$ were approximately 7-and 5-fold higher, respectively, when abiraterone acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17- and 10-fold higher, respectively, when abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal. Given the normal variation in the content and composition of meals, taking abiraterone acetate with meals has the potential to result in increased and highly variable exposures. Therefore, no food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken. The tablets should be swallowed whole with water.

2. Distribution: Abiraterone is highly bound (>99%) to the human plasma proteins, albumin and alpha-1 acid glycoprotein. The apparent steady-state volume of distribution (mean ± SD) is 19,669 ± 13,358 L. In vitro studies show that at clinically relevant concentrations, abiraterone acetate and abiraterone are not substrates of P-glycoprotein (P-gp) and that abiraterone acetate is an inhibitor of P-gp. No studies have been conducted with other transporter proteins.

3. Metabolism: Following oral administration of 14C-abiraterone acetate as capsules, abiraterone acetate is hydrolyzed to abiraterone (active metabolite). The conversion is likely through esterase activity (the esterases have not been identified) and is not CYP mediated. The two main circulating metabolites of abiraterone in human plasma are abiraterone sulphate (inactive) and N-oxide abiraterone sulphate (inactive), which account for about 43% of exposure each. CYP3A4 and SULT2A1 are the enzymes involved in the formation of N-oxide abiraterone sulphate and SULT2A1 is involved in the formation of abiraterone sulphate.

4. Excretion: In patients with metastatic CRPC, the mean terminal half-life of abiraterone in plasma (mean ± SD) is 12 ± 5 hours. Following oral administration of 14C-abiraterone acetate, approximately 88% of the radioactive dose is recovered in feces and approximately 5% in urine

The major compounds present in feces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

c. ADVERSE EFFECTS

1. Refer to the package insert or manufacturer's website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

Adverse Events with Possible Relationship to Abiraterone Acetate		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
CARDIAC DISORDERS		
	Hypertension	Cardiac failure
	Arrhythmias	
	Chest pain or discomfort	
GASTROINTESTINAL DISORDERS		
	Diarrhea	
	Dyspepsia	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Edema		
Peripheral edema		
Pitting edema		
Generalized edema		
INFECTIONS AND INFESTATIONS		
	Urinary tract infection	Urosepsis
	Upper respiratory tract infection	
INVESTIGATIONS		
	Hypokalemia	
	Hypophosphatemia	
	Increased ALT	
	Increased AST	
	Increased triglycerides	
	Increased total bilirubin	
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS		
Arthritis	Fractures	
Arthralgia		
Joint swelling		
Joint stiffness		
Muscle spasms		
Musculoskeletal pain		
Myalgia		
Musculoskeletal discomfort		
Musculoskeletal stiffness		
RENAL AND URINARY DISORDERS		
	Urinary frequency	
	Nocturia	

Adverse Events with Possible Relationship to Abiraterone Acetate		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	Non-infectious pneumonitis
VASCULAR DISORDERS		
	Hot flash	

2. Warnings and Precautions

Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess: Use abiraterone acetate with caution in patients with a history of cardiovascular disease. Abiraterone acetate may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. The safety of abiraterone acetate in patients with left ventricular ejection fraction <50% or NYHA Class III or IV heart failure has not been established because these patients were excluded from the randomized clinical trial. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month.

Adrenocortical Insufficiency: Adrenocortical insufficiency has been reported in clinical trials in patients receiving abiraterone acetate in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with abiraterone acetate. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Cardiovascular Adverse Reactions: The majority of arrhythmias were Grade 1 or 2. Grade 3-4 arrhythmias occurred at similar rates in the two arms. There was one death associated with arrhythmia and one patient with sudden death in the abiraterone acetate arm. No patients had sudden death or arrhythmia associated with death in the placebo arm. Cardiac ischemia or myocardial infarction led to death in 2 patients in the placebo arm and 1 death in the abiraterone acetate arm. Cardiac failure resulting in death occurred in 1 patient on both arms.

Hepatotoxicity: Drug-associated hepatotoxicity with elevated ALT, AST, and total bilirubin has been reported in patients treated with abiraterone acetate. Across all clinical trials, liver function test elevations (ALT or AST increases of > 5X ULN) were reported in 2.3% of patients who received abiraterone acetate, typically during the first 3 months after starting treatment. In the Phase III trial, patients whose baseline ALT or

AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5X ULN, or elevations in bilirubin > 3X ULN were observed, abiraterone acetate was withheld or discontinued. In two instances marked increases in liver function tests occurred. These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40X ULN and bilirubin elevations 2 to 6 X ULN. Upon discontinuation of abiraterone acetate, both patients had normalization of their liver function tests and one patient was re-treated with abiraterone acetate without recurrence of the elevations.

3. Pregnancy and Lactation: Pregnancy Category X. Abiraterone acetate is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the potential risk for pregnancy loss. Women of childbearing potential should be advised to avoid becoming pregnant during treatment with abiraterone acetate. It is not known if abiraterone acetate is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from abiraterone acetate, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

4. Drug Interactions: In vitro studies with human hepatic microsomes showed that abiraterone is a strong inhibitor of CYP1A2 and CYP2D6 and a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5. In an *in vivo* drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively when dextromethorphan 30 mg was given with abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily). The AUC for dextrorphan, the active metabolite of dextromethorphan, increased approximately 1.3 fold. For this reason, co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine) should be avoided.

   Based on in vitro data, abiraterone acetate is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, in vivo. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during abiraterone acetate.

   In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg of abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with abiraterone acetate.

d. DOSING & ADMINISTRATION

1. Dosing – See Treatment Plan Section 7.0

2. Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken. The tablets should be swallowed whole with water. Exposure of abiraterone increases up to 10 fold when abiraterone acetate is taken with meals.

a. STORAGE & STABILITY

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]. Based on its mechanism of action, abiraterone acetate may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle abiraterone acetate without protection, e.g., gloves.

b. HOW SUPPLIED

1. Abiraterone acetate is supplied as a tablet in 250 mg strength. The tablets are oval, and white to off-white.

2. Abiraterone acetate is investigational for this study and will be supplied free of charge to patients by Janssen Scientific Affairs, LLC for distribution by Biologics.

3. Drug Ordering: Abiraterone acetate may be requested by the Principal Investigator (or their authorized designee) at each participating institution by completing and faxing the Biologics Drug Request for **S1014** (see **S1014** abstract page on the SWOG website) once patient has been registered. **Allow 7 business days for shipment of drug from receipt of the Biologics Drug Request Form. Form should be faxed to the number on the form.** Orders received before 2 p.m. EST Monday through Friday will be processed and shipped for next business day delivery. Orders received after 2 p.m. EST Monday through Friday will be processed and shipped the next business morning. Shipments will be sent via Federal Express for Priority Overnight delivery. Biologics will be closed the following holidays: New Years Eve, New Years Day, Memorial Day, Independence Day, Labor Day, Thanksgiving, Thanksgiving Friday, Christmas Eve and Christmas Day. The abiraterone acetate to be supplied for this protocol is intended for clinical trial use only.

Initial Shipments: Once a patient is registered, the site will fax a completed Drug Request Form to Biologics at 919-256-0794. Upon receipt of completed and faxed Drug Request Form, Biologics Inc. will:

- Place a call or email to the site confirming the Drug Request Form was received, while providing the estimated day and time of arrival for the study drug. At this time, Biologics will confirm the patient's dose for the first three - 28 day cycles and confirm the Drug Request Form is completed.

- Prepare an initial shipment supply for the patient's first three - 28 day cycles (based on a dose provided

by the registration/site [1,000 mg]). Shipments will include 3 bottles of study drug to complete the 28 day cycle at a dose of 1,000 mg PO QD x 28 days. Drug supply will be dispensed in a bottle with patient specific labeling. Each bottle will contain 120 tablets of study drug.

Follow up Calendar. Biologics will contact the site approximately 14 days prior to the next cycle start date to arrange the next shipment.

Subsequent Shipments: Biologics will contact the site approximately 14 days prior to the next cycle due date to request a completed Drug Request Form and the next cycle start date to arrange the next shipment.

Upon receipt of completed and faxed Drug Request Form, Biologics Inc. will

- Place a call or email to the site confirming the Drug Request Form was received, while providing the estimated day and time of arrival for the study drug. At this time, Biologics will confirm the patient's dose and number of cycles requested.

- Prepare the subsequent shipment supply for the patient for the number of cycles requested, based on the dose provided by the site. Shipments will include 3 bottles of study drug to cover the next 3 cycles. Drug supply for each cycle will be dispensed in a bottle with patient specific labeling. Each bottle will contain 120 tablets of study drug based on the patient's current dose. Date of next shipment is entered into a Follow up Calendar. Biologics will contact the site approximately 14 days prior to the next cycle start date to arrange the next shipment.
- Process and ship authorized and completed orders "same day" of order receipt if received before 2:00 p.m. E.T Monday through Friday. Authorized and completed orders received after 2:00 pm E.T. Monday through Friday will be processed and shipped the next business morning.

  All drug orders are shipped via FedEx for Priority Overnight delivery. Study Drug is shipped in a Biologics, Inc. branded box with appropriate ice to maintain temperature stability. Each shipment will include a temperature monitoring device with instructions for interpretation by recipient. This will ensure that the temperature was maintained during transit. Enclosed will be a packing slip that includes the quantity of drug provided with a section to be completed once received by the site coordinator. This section includes confirmation of drug receipt, verification of package contents, and instruction to fax the completed packing slip to Biologics.

- Each shipment includes a patient label on the Ziploc bags with the following information:
  - Study number and Date Dispensed

- IND Caution statement and/or local regulatory statements 'Investigational Drug'
- Drug Identification, Lot number, Expiration
- Subject ID number
- Subject Initials
- Storage conditions
- Dosing Instructions

Packages are tracked by Biologics, Inc. until confirmed delivered and delivery exceptions are managed with the highest level of urgency to ensure therapy start date adherence. Packing slips with the shipment tracking number included will be faxed to the designated site coordinator for all shipments.

Once study drug is received at the clinical trial site:

- The designated site coordinator validates contents of package matches information provided on packing slip, signs off on the packing slip, and faxes completed form to Biologics to validate shipment has been received and is accurate.

  The order transaction is completed by Biologics, Inc. by entering the receipt confirmation into the CTS database and placing the signed packing slip in the study file.

  Year 1 Example of Biologics Follow up Calendar and Shipment Schedule (to continue for 3 years)

Cycle(s)	Months 1-3	Months 4-6	Months 7-9	Months 10-12
Follow up Date by Biologics (call site)	n/a	14 Days prior to Start of Cycle 4 (Day 70)	14 Days prior to Start of Cycle 7 (Day 182)	14 Days prior to Start of Cycle 10 (Day 266)
Next Shipment Due Date	n/a	Month 6	Month 9	Month 12

4. Drug Handling and Accountability

a. The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return or disposal of all drug received from the supplier using the NCI Drug Accountability Record Form (DARF) available at http://ctep.cancer.gov.

b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF.

5. Drug Returns: Unused drug supplies should NOT be returned. Unused drug should be disposed of per local institutional guidelines.

6. Questions about drug orders, transfers, returns, or accountability should be addressed to Karl Buer at Biologics, Inc. (800/693-4906 or kbuer@biologicstoday.com).

3.2 Prednisone (NSC-10023)

a. DESCRIPTION

Prednisone is a glucocorticoid which is rapidly absorbed from the GI tract.

b. TOXICOLOGY

Human Toxicology: Possible adverse effects associated with the use of prednisone are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, mood swings, depression, exacerbation of infection (e.g., tuberculosis), exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer disease, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or other hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms of adrenal insufficiency including fever, myalgia and arthralgia. Phenytoin, phenobarbitol, and ephedrine enhance metabolic clearance of corticosteroids.

Corticosteroids should be used cautiously in patients with hypothyroidism, cirrhosis, ocular herpes simplex, existing emotional instability or psychotic tendencies, nonspecific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, peptic ulcer disease, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Immunization procedures (especially smallpox vaccination) should not be undertaken in patients on corticosteroids.

c. PHARMACOLOGY

Pharmacokinetics: Natural and synthetic glucocorticoids are readily and completely absorbed from the GI tract. Prednisone is slightly soluble in water. Glucocorticoids have salt-retaining properties. The anti-inflammatory property of this drug is due to a down-regulation of the body's immune system and as a consequence it can suppress the body's response to viral as well as bacterial infections.

Formulation: Prednisone is available in 2.5 mg, 5 mg, 10 mg, 20 mg and 50 mg tablets.

Storage and Stability: Prednisone should be stored at room temperature.

Administration: Prednisone is administered orally.

Supplier: Prednisone is commercially available and should be purchased by third party. Prednisone will not be supplied by the NCI.

Please refer to the Physician Desk Reference and package insert for complete information.

4.0 STAGING CRITERIA

Distant metastasis (M)

M1: Distant metastasis

NOTE: Regional lymph node metastasis by itself is insufficient for the classification of M1 disease.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the **S1014** Prestudy Form and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 2 weeks later would be considered Day 14. This allows for efficient patient scheduling without exceeding the guidelines. If Day 14, 28, 42, or 56 falls on a weekend or holiday, the limit may be extended to the next working day.

5.1 Disease Related Criteria

a. All patients must have a histologically or cytologically proven diagnosis of adenocarcinoma of the prostate. Small cell or neuroendocrine prostate cancer is not allowed. All patients must have had metastatic (M1) (see Section 4.0) disease as evidenced by soft tissue and/or bony metastases at the time of initiation of androgen deprivation therapy (ADT). Patients must have at least one of the following at the time they started androgen deprivation therapy:

(1) Visceral disease (liver, lung, other viscera),
(2) Bone metastases to sites in either the axial (spine, pelvis, ribs, skull) and/or the appendicular (clavicle, humerus, femur) skeleton,
(3) Distant lymph node disease (e.g. above the aortic bifurcation, etc.).

b. Patients must have a Zubrod performance status of 0 - 2 (see Section 10.3).

c. All patients must be receiving androgen deprivation therapy (e.g., GNRH agonist with or without antiandrogen) prior to entering this study. Degarelix, a FDA-approved GNRH antagonist, is an acceptable form of androgen deprivation therapy. Bilateral surgical orchiectomy is also acceptable.

d. Only patients with a suboptimal response to initial androgen deprivation therapy (ADT) induction, with a PSA of > 4 ng/ml between 6-12 months from starting ADT for metastatic disease, will be eligible. Documentation of failure to achieve this PSA of ≤ 4 ng/ml must be within 28 days of registration. The PSA must be obtained after any applicable antiandrogen washout period.

If the PSA is declining or stable (defined as a PSA rise ≤ 0.1 ng/ml from nadir) and the patient is on an antiandrogen, they must remain on the antiandrogen (see Section 7.3). Patients with stable or declining PSA who have had previous antiandrogen exposure, but are not taking an antiandrogen at the time of registration, must wait at least 6 weeks from the last antiandrogen dose before

registration and still demonstrate a stable or falling PSA which is > 4 ng/ml by month 12, in order to be eligible.

If the PSA is rising and they are on an antiandrogen, formal antiandrogen washout must be performed (4 weeks for flutamide and 6 weeks for bicalutamide and nilutamide with no evidence of a falling PSA after washout).

e. Patients who have any measurable disease must have it assessed by an abdominal/pelvic CT within 28 days prior to registration. All non-measurable disease must be assessed by a bone scan within 42 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form.

f. Patients with a history of prior neoadjuvant or adjuvant GNRH agonist/antagonist therapy (related to previous surgery or radiation) are eligible provided they finished this therapy at least two years prior to registration. Prior use of finasteride or dutasteride is allowed as long as it is discontinued at least 6 weeks prior to registration. Prior enrollment to **S0925** (either arm) is not exclusionary.

g. Patients with a history of brain metastases or who currently have treated or untreated brain metastases are not eligible. Patients with clinical evidence of brain metastases must have a brain CT or MRI negative for metastatic disease within 56 days prior to registration

h. Patients must not have received any prior cytotoxic chemotherapy or radiopharmaceuticals for prostate cancer. Previous ketoconazole therapy for the treatment of prostate cancer is not allowed. Patients requiring more than 10 mg a day of prednisone for another medical indication are not eligible. Patients must not have received any prior Provenge.

5.2 Prior/Concurrent Therapy Criteria

a. Patients must not have received any prior cytotoxic chemotherapy or radiopharmaceuticals for prostate cancer. Previous ketoconazole therapy for the treatment of prostate cancer is not allowed. Patients requiring more than 10 mg a day of prednisone for another medical indication are not eligible. Patients must not have received any prior Provenge.

b. Patients may have received prior radiation therapy or surgery. However, at least 28 days must have elapsed since completion of radiation therapy or surgery and patient must have recovered from all side effects.

c. Patients must not be planning to receive any concurrent cytotoxic chemotherapy, surgery, or radiation therapy during protocol treatment. Hormonal-acting agents (including diethylstilbestrol/DES, aldosterone, PC-SPES, and spironolactone) are forbidden during the trial and must be stopped prior to registration. No washout period will be required for any of these agents. However, any investigational products must be stopped at least 28 days (4 week washout) prior to registration.

5.3 Clinical/Laboratory Criteria

a. Patient must have a testosterone value of < 50 ng/dl obtained within 28 days prior to registration.

b. Patients must have absolute neutrophil count (ANC) ≥ 1,500/mcL, platelet count ≥ 100,000/mcL and hemoglobin ≥ 10 g/dl obtained within 28 days prior to registration.

c. Patients must have serum creatinine ≤ 1.5 x the institutional upper limit of normal (ULN) or a calculated creatinine clearance of ≥ 60 ml/min obtained within 28 days prior to registration.

$$\text{Calculated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)}}{72 \times \text{creatinine (mg/dl)}}$$

d. Patients must have a bilirubin ≤ 1.5 x ULN (unless documented Gilbert's disease), SGOT (AST) and SGPT (ALT) < 1.5 x ULN obtained within 28 days prior to registration.

e. Patients must have potassium ≥ 3.5 mmol/L obtained within 28 days prior to registration.

f. Patients must be able to take oral medication without crushing, dissolving or chewing tablets. Patients must not have a history of gastrointestinal disorders (medical disorders or extensive surgery) that may interfere with the absorption of abiraterone acetate.

g. Patients with active or symptomatic viral hepatitis or chronic liver disease are not eligible. Patients must not have moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment (see Appendix 18.5).

h. Patients must have well controlled blood pressure defined as a systolic blood pressure < 160 mmHg and diastolic blood pressure < 95 mmHg at the time of the screening visit. Patients with a history of hypertension are eligible provided blood pressure is controlled within these parameters with anti-hypertensive treatment.

i. Patients with a history of New York Heart Association Class III and IV heart failure (see Appendix 18.2) or a known left ventricular ejection fraction (LVEF) of < 50% are not eligible.

j. Patients must not have known allergies, hypersensitivity, or intolerance to abiraterone acetate, prednisone or their excipients.

k. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.

l. Patients who have partners of child-bearing potential must be willing to use a method of birth control with adequate barrier protection during the study and for one week after the last study drug administration.

5.4 Regulatory Criteria

a. All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

b. As a part of the OPEN registration process (see Section 13.3 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

There are no stratification factors for this study.

7.0 TREATMENT PLAN

For treatment or dose modification related questions, please contact Dr. Thomas Flaig at 303/724-3808 or Dr. Maha Hussain at 734/936-8906. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy #38).

7.1 Good Medical Practice

The following tests (and/or assessments) are recommended within 28 days prior to registration in accordance with Good Medical Practice. Results of these tests do not determine eligibility and minor deviations from normal limits would be acceptable if they do not affect patient safety in the clinical judgment of the treating physician. If there are significant deviations in these tests/assessments that could impact on patient safety, it is highly recommended that the registering investigator discuss the patient with the Study Coordinator prior to patient registration.

Pre-study tests for good medical practice include the following:

a. Alkaline phosphatase obtained,

Patients must have recovered from major infections. In the opinion of the investigator the patient must not have any significant active concurrent medical conditions which would exclude protocol treatment.

b. Patients must not have a history of pituitary or adrenal dysfunction.

c. Patients should not have any medical condition, which in the opinion of the investigator places the patient at undue risk of potentially serious complications while on therapy. These would include: untreated diabetes mellitus, infection, or concurrent medications that alter cardiac conduction.

7.2 Treatment Schedule

AGENT	DOSE	ROUTE	DAYS	DURATION
Abiraterone acetate	1,000 mg (4 tablets)	PO	Daily (On an empty at least 2 hours after and 1 hour before eating.)	Until disease progression
Prednisone	5 mg	PO	5 mg twice daily	Until disease progression

Abiraterone acetate: Four 250 mg tablets (1,000 mg) must be taken orally on an empty stomach at least 2 hours after and 1 hour before a meal any time up to 10:00 p.m. every day. Abiraterone acetate may be taken with prednisone. A cycle of treatment for this study is 28 days.

Patients will continue treatment until disease progression or other reason for discontinuation of protocol treatment (see Section 7.5).

7.3 Prior Anti-Androgen Use

Patients will have received androgen blockade with GNRH agonist (goserelin acetate or leuprolide acetate) or a GNRH antagonist (Degarelix) per the treating physician and this will be given continuously throughout protocol treatment. Bilateral surgical orchiectomy is also acceptable.

Since stopping an antiandrogen may impact the primary endpoint of the study, there are specific instructions about the use of antiandrogens for patients registered with a stable or declining PSA (≤ 0.1 ng/ml rise over nadir) and taking antiandrogen therapy (e.g. flutamide, bicalutamide, nilutamide) at the time of registration. These patients must be willing to continue on this therapy without washout for the duration of protocol treatment.

7.4 Intake Calendar

Abiraterone acetate and prednisone compliance will be recorded by patients on the Intake Calendar (see Appendix 18.3). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking compliance. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

7.5 Concomitant Medications

The use of supportive care medications is allowed according to institutional standards. GNRH agonist (e.g. goserelin acetate or leuprolide) or antagonist (Degarelix) must be continued throughout the study and are considered a standard of care treatment for this patient population.

Several medications are specifically allowed. Conventional multi-vitamins are allowed. Additional glucocorticoid use, beyond prednisone 5 mg twice daily, is allowed as deemed medically necessary. Bisphosphonates and denosumab are allowed, provided this therapy was started prior to registration. Transfusions and hematologic growth factors are allowed in accordance with institutional guidelines. Antiandrogens (e.g. flutamide, bicalutamide, and nilutamide) are to be continued in certain circumstances (see Section 5.1d for details). Since the cessation of an antiandrogen may impact PSA, antiandrogens are not to be stopped while on protocol. If the antiandrogen needs to be stopped for safety or other reasons, patient must be taken off protocol treatment.

Several medications are specifically disallowed. Five-alpha reductase inhibitors (e.g. finasteride and dutasteride) are not permitted. Other excluded therapies include ketoconazole, diethylstilbestrol/DES, aldosterone, spironolactone, and PC-SPES. Other **excluded treatments include chemotherapy, immunotherapy, and radiopharmaceuticals or any other therapy intended to treat prostate cancer. In vitro studies with human hepatic microsomes showed that abiraterone is a strong inhibitor of CYP1A2 and CYP2D6 and a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug. Based on in vitro data, abiraterone acetate is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, in vivo. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during abiraterone acetate treatment.**

Please also see Appendix 18.4 for more details regarding specific drugs that may interact with abiraterone acetate in reference to these guidelines.

7.6 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration (as defined in Sections 10.1-10.2).

b. Unacceptable toxicity.

c. The patient may withdraw from the study at any time for any reason.

d. Delay of greater than four weeks beyond the planned abiraterone acetate treatment date or the requirement of more than two dose reductions of abiraterone acetate.

e. For the subset of patients taking an antiandrogen at baseline and continuing it during protocol treatment (see Section 5.1d), these patients must be taken off protocol treatment if they stop taking the antiandrogen.

NOTE: Patients are not to be removed from protocol treatment for PSA progression only. In order to be considered a "responder" with regard to the primary endpoint, a patient will need to achieve a confirmed PSA of < 0.2 ng/ml by 12 months. However, a non-responding patient who is judged to have a clinical benefit from the protocol treatment may continue to receive treatment until one of the specific criteria above are reached. In addition, for the subset of patients taking an antiandrogen at registration and continuing this treatment (see Section 5.1d), the antiandrogen cannot be discontinued while on the protocol, as this may affect the PSA kinetics.

7.7 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the study forms.

7.8 Follow Up Period

8.0 DOSAGE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 Dose Levels of Study Drugs

Dose levels are defined below:

Dose Level	Abiraterone acetate	Prednisone
0	1,000 mg daily	5 mg twice daily
-1	750 mg daily	5 mg twice daily
-2	500 mg daily	5 mg twice daily

8.3 Abiraterone Acetate Dose Modifications

An adverse event, using the common terminology definition, is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment that may or may not be related to that treatment. A dose reduction will be pursued for any serious adverse event, defined as any Grade 4 toxicity and also for any Grade 3 toxicity that is believed to potentially impact the safety of the participant. The dose of abiraterone will not be re-escalated once a dose reduction has occurred. Abiraterone will be held and the subjects followed until resolution of any Grade 3 or 4 adverse event to ≤ Grade 1. Asymptomatic laboratory abnormalities would not be considered a serious adverse event unless the investigator believes it may potentially impact the participant's safety or unless it is specifically addressed separately in the protocol (e.g. hypokalemia and liver test abnormalities).

Due to the known side effect of hypokalemia, oral replacement of potassium is to be started with grade 1 hypokalemia. With Grade 3 or 4 hypokalemia, abiraterone acetate is to be held until it resolves to ≤ Grade 1 and IV potassium replacement is to be given with appropriate monitoring.

For patients who develop hepatotoxicity during treatment with abiraterone acetate (ALT and/or AST greater than 5X ULN or total bilirubin greater than 3X ULN), interrupt treatment with abiraterone acetate. Treatment may be restarted at a reduced dose of 750 mg once daily (dose level -1) following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN. For patients who resume treatment, monitor serum transaminases and bilirubin at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the dose of 750 mg once daily, re-treatment may be restarted at a reduced dose of 500 mg once daily (dose level -2) following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN.

If hepatotoxicity recurs at the reduced dose of 500 mg once daily, discontinue treatment with abiraterone acetate. The safety of abiraterone acetate re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown and patients who develop liver function test abnormalities to this degree will be removed from the study.

8.4 Prednisone Dose Modifications

Prednisone is included in this regimen primarily as a safety medication to reduce the potential incidence of mineralocorticoid excess from abiraterone acetate. For this reason, the prednisone cannot be dose reduced or held without holding the abiraterone acetate. If Grade 3 or 4 toxicity develops which is known to be related to prednisone (e.g. hyperglycemia) and this is believed to potentially impact the safety of participation, both prednisone.

8.5 Dose Modification Contacts

For treatment or dose modification related questions, please contact Dr. Thomas Flaig at 303/724-3808 or Dr. Maha Hussain at 734/936-8906.

8.6 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Coordinator, the NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 Calendar

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REQUIRED STUDIES	PRE	Cycle 1				Cycle 2				Cycle 3				Cycle 4				F/U Prior to	F/U After
	STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Prog	Prog
PHYSICAL																			
History & Physical Exam	X	X				X				X				X				X	X
Weight and Performance Status	X	X				X				X				X					X
Blood Pressure	X	X				X				X				X				X	
Disease Assessment ≠	X													X					
Toxicity Notation π		X		X		X		X		X		X		X					X
Adverse Event Assessment π		X				X				X				X					
LABORATORY																			
Serum PSA *	X*	X				X				X				X				X	X
Serum Testosterone	X																		
CBC/Differential/ Platelets/Hemoglobin	X	X				X				X				X					X
Creatinine	X	X				X				X				X					X
Potassium	X	X				X				X				X					X
Bilirubin	X	X		X		X		X		X		X		X					X
Albumin	X	X		X		X		X		X		X		X					X
SGOT and SGPT	X	X		X		X		X		X		X		X					X
Alkaline Phosphatase β	X	X		X		X		X		X		X		X					X

Calendar continued on next page. Click here for footnotes.

		¶												Ω				Σ	£
		Cycle 1				Cycle 2				Cycle 3				Cycle 4				F/U	F/U
REQUIRED STUDIES	PRE	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Prior to	After
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Prog	Prog
X-RAYS AND SCANS																			
CT or MRI of Brain §	X																		
CT of Abdomen & Pelvis ≠	X													X				X	
Bone Scan ≠	X													X				X	
TREATMENT (see Section 7.0)																			
Abiraterone acetate ¥		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Prednisone ¥		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

Footnotes:

≠ Radiographic assessment will be done every 12 weeks by the same method used to document metastatic disease at baseline and as clinically indicated. REMEMBER, PSA RESPONSE SHOULD BE CONFIRMED BY A SECOND PSA DETERMINATION AT LEAST 4 WEEKS AFTER A PSA RESPONSE HAS BEEN NOTED.

§ Only if clinically indicated (see Section 5.2g).

¥ Treatment will be given daily and will continue until disease progression or other reason for discontinuation of protocol treatment see Section 7.5).

¶ Laboratory assessments and exam do not need to be repeated on Day 1, Week 1 if the prestudy laboratory assessments and exam was done within 7 days.

Ω Protocol treatment and assessment parameters will continue at these intervals (monthly exam and laboratory assessment and radiographic assessment every 6 months) until off protocol treatment (see Section 7.5). Scans may be performed more frequently than every 6 months at the investigator's discretion or with any signs or symptoms of progression.

Σ Once off protocol treatment and prior to progression, physical exams, x-rays, scans and PSA for disease assessment should be performed at least every 6 months or earlier as clinically indicated to assess patient for progression for up to 3 years from registration.

£ After disease progression, follow-up will occur at the discretion of the treating investigator. Survival status will be assessed for up to 3 years from registration.

* See Section 5.1d

π A toxicity notation is required whenever a laboratory assessment is done (every 2 weeks for the first 3 months, then monthly) and at the last study visit. An adverse event assessment with a physical examination must be done monthly. Patients who experience adverse events of ≥ Grade 3 severity must be followed until resolution or stabilization of the adverse event.

β Result of this test does not determine eligibility, but is recommended prior to registration in accordance with Good Medical Practice (see Section 7.1).

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Progression Criteria

PSA assessments will not be used to determine progression. One or more of the following must occur: Unequivocal progression of disease in the opinion of the treating physician (an explanation must be provided). Progressive disease as defined by RECIST 1.1 or the prostate cancer working group bone scan progression criteria as described below. Death due to disease without documented progression and without symptomatic deterioration (see Section 10.2) will be considered progression.

When bone scan progression is the only indicator of progression, at least 2 new bone scan lesions must be observed, compared to study entry exam. When progression on bone scan is observed at the first scheduled exam (at 12 weeks of protocol treatment), without clear soft tissue or symptomatic progression, this finding should be confirmed at least 6 weeks later with the development of additional new lesions, to exclude flare phenomenon (for a total of 4 or more lesions on the confirmatory bone scan). When progression occurs on bone scans beyond the first assessment point (at 12 weeks of protocol treatment), the appearance of 2 or more new lesions compared to baseline is still required. A confirmatory bone scan should generally be done in this situation at least 6 weeks later, unless there is the appearance of multiple new lesions in which case confirmation is not required, based on investigator assessment. If a confirmatory scan is not planned, the SWOG Study Coordinator should be contacted to discuss. *(23)* An increase in size or intensity of a known lesion is not sufficient for progression criteria. Subjects will also be deemed to have progressed if they require surgery to the bone, radiation therapy to the bone, or any other local bone-directed treatment. Progression will be calculated from the time of the first bone scan with a new metastatic lesion, not the confirmatory scan.

10.2 Symptomatic Deterioration

Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression.

Notes: (1) In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), either symptoms must persist beyond 4 weeks or there must be additional evidence of progression. (2) Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed. (3) For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. (4) Appearance or worsening of pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin.

10.3 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	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.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.

3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.4 Time to Treatment Failure

From date of registration to date of first documentation of progression or symptomatic deterioration (as defined above), early discontinuation of treatment, or death due to any cause. Patients last known not to have failed treatment are censored at the date of last contact.

10.5 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

10.6 Undetectable PSA

Undetectable PSA is the primary endpoint and defined as a PSA level of ≤ 0.2 ng/ml, confirmed by a second measurement with a PSA ≤ 0.2 ng/ml at least 4 weeks later, without any evidence for progression. The primary endpoint will be assessed on an ongoing basis for the first year on study. Patients not responding within the first year on study will be classified as non-responders for the primary endpoint. The PSA response rate stratified by those taking an antiandrogen and those who are not will also be reported.

10.7 PSA Partial Response

A PSA partial response (PSA PR) is a secondary endpoint and defined as a ≥ 50% decrease in the PSA from the baseline assessment (after any antiandrogen washout period just prior to registration for patients registered with a rising PSA), confirmed by a second PSA measurement at least 4 weeks later. We will also compare the number of subjects who obtain a confirmed PSA reduction of 90% or more compared to their baseline, a confirmed PSA reduction of 1.0 ng/ml or more from their baseline, and the number who achieve a PSA of < 4 ng/ml.

11.0 STATISTICAL CONSIDERATIONS

11.1 Accrual Rate

The accrual rate is anticipated to be 30 patients per year, based on recent accrual of a subset of patients from **SWOG-9346.**

11.2 Analysis of Primary Endpoint

The main objective of this study is to test whether this regimen has promise in terms of rates of undetectable PSA. If the proportion of men with undetectable PSA is 20% or greater, the regimen would be of further interest, whereas further testing would not be pursued if the proportion of men with undetectable PSA is 5% or less. Six or more subjects with undetectable PSA out of the total 38 eligible patients would indicate that further study of this regimen is warranted. **The design has a significance level (chance of falsely determining further study is warranted of a treatment with < 5% response rate) of 5.0% and a power (probability of correctly identifying the agent as warranting further study for a likely response rate of > 20%) of 90%.**

11.3 Analysis of Secondary Endpoints

Thirty-eight eligible patients will be sufficient to estimate the PSA undetectable and normalization rate, the progression-free survival and the overall survival at a specified time point, and the probability of a particular adverse event to within +/- 16% (95% confidence interval). Any toxicity occurring with at least a 5% probability is likely to be seen at least once (83%).

The 20% alternative hypothesis is based on the observation that approximately 20% of castrate-resistant prostate cancer (CRPC) patients treated with abiraterone acetate and prednisone were observed to have a > 90% PSA reduction, indicating that dramatic PSA responses may be expected in 20% of traditional CRPC patients treated. *(22)*

11.4 Data and Safety Monitoring Committee Oversight

There is no formal data and safety monitoring committee for single arm Phase II studies. Toxicity and accrual monitoring are done routinely by the Study Coordinator, study Statistician and the Disease Committee Chair. Endpoint monitoring is done by the study Statistician and Study Coordinator. Accrual reports are generated weekly and formal toxicity reports are generated every 6 months. In addition, the Statistical Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer, and Study Coordinator monitor toxicities on an ongoing basis.

12.0 DISCIPLINE REVIEW

There will be no formal discipline review done in conjunction with this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than ten working days prior to planned start of treatment).

13.2 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.3 Registration procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is a web-based application and can be accessed at https://open.ctsu.org, or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should refer to Section 5.0 to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site.
- To perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.4 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for ALL patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master Forms can be found on the protocol abstract page (www.swog.org) and (with the exception of the consent form and the Registration Worksheet) must be submitted online via the web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. SWOG institutions must submit data electronically via the Web by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Next, click on the *Data Submission* link and follow the instructions. For new users, the link to a "Starter Kit" of help files may be found by clicking on the Starter Kit link at the Members' logon page.

To submit data via the web the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page). For other difficulties with the CRA Workbench, please email *technicalquestion@crab.org*.

b. If you need to submit data that are <u>not</u> available for online data submission, the only alternative is via facsimile. Should the need for this occur, institutions may submit data via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use cover sheet for faxed data. Please make sure that each page of all faxed data include the SWOG patient number, study ID and patient initials.

14.4 Data Submission Overview and Timepoints

a. <u>WITHIN 7 DAYS OF REGISTRATION</u>:

Submit copies of the following:

<u>S1014</u> Prestudy Form

Baseline Tumor Assessment Form

<u>S1014</u> Prostatic Specific Antigen Reporting Form

Pathology Report

Radiology Reports from all scans performed to assess disease at baseline

b. <u>EVERY TWELVE WEEKS UNTIL PROGRESSION; AT TIME OF PROGRESSION; AND AT CONFIRMATION OF PSA RESPONSE</u>:

<u>S1014</u> Prostate Specific Antigen Reporting Form

c. <u>WITHIN 7 DAYS OF COMPLETION OF EACH CYCLE WHILE ON PROTOCOL TREATMENT:</u>

<u>S1014</u> Treatment Form

<u>S1014</u> Adverse Event Form

d. EVERY TWELVE WEEKS UNTIL PROGRESSION WHILE ON PROTOCOL TREATMENT (AT TIME OF DISEASE ASSESSMENT):

Follow-Up Tumor Assessment Form

Radiologic Assessment Reports

e. WITHIN 14 DAYS OF DISCONTINUATION OF ALL PROTOCOL TREATMENT:

Off Treatment Notice

Final **S1014** Treatment Form

Final **S1014** Adverse Event Form

S1014 Prostatic Specific Antigen Reporting Form

f. AFTER OFF ALL PROTOCOL TREATMENT, EVERY SIX MONTHS FOR THREE YEARS OR UNTIL DEATH:

Follow Up Form

g. WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

S1014 Treatment Form and **S1014** Adverse Event Form(if the patient was still on protocol treatment); OR Follow-Up Form (if the patient was off protocol treatment) documenting date, site and method for determining progression/relapse; **S1014** Prostate Specific Antigen Reporting Form; Off Treatment Notice (if the patient was still on protocol treatment), and Follow-Up Tumor Assessment Form.

h. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Notice of Death and a final S1014 Treatment Form and S1014 Adverse Event Form (if the patient was still on protocol treatment) or Follow-Up Form (if the patient was off protocol treatment) documenting death information.

15.0 SPECIAL INSTRUCTIONS

There are no special instructions for this study.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also Appendix 18.1 for general and background information about expedited reporting.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to the SWOG Operations Office by telephone at 210-614-8808 or by email at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification that was made by phone or using adr@swog.org must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in Table 16.1.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent used in this study is abiraterone acetate. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] Abiraterone Acetate.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or [Section 16.1f.]

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a Non-CTEP IND:**

1. **Group-specific instructions.**

Supporting Documentation Submission - Within **5 calendar days** submit the following to the SWOG Operations Office by fax to 210-614-0006 or mail to the address below:

- Printed copy of the first page of the CTEP-AERS report
- Copies of clinical source documentation of the event
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center, copies of Off Treatment Notice and/or Notice of Death.

2. The adverse event listed below does not require expedited reporting via CTEP-AERS:

- Grade 4 myelosuppression

g. **Reporting Secondary Malignancy, including AML/ALL/MDS**

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

SWOG requires all secondary malignancies that occur following treatment with an agent under a non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the *initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.*

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. A copy of the report and the following supporting documentation must also be submitted to the SWOG Operations Office within 30 days:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

SWOG
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

17.0 BIBLIOGRAPHY

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18.0 APPENDIX

18.1 Determination of Expedited Adverse Event Reporting Requirements

18.2 Intake Calendar

18.3 Potential Drug Interaction with Abiraterone Acetate

18.4 Child-Pugh Classification (CPC) of Liver Dysfunction

18.1 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.1.

All serious adverse events determined to be reportable to the Institutional Review Board responsible for the oversight of the patient must be reported according to local policy and procedures. Documentation of this reporting should be maintained for possible inspection during quality assurance audits.

- ***Steps to determine if an adverse event is to be reported in an expedited manner*** (*This includes all events that occur while on treatment or within 30 days of the last dose of protocol treatment.*)

Step 1: Determine whether the patient has received an investigational agent, commercial agent, or a combination of investigational and commercial agents.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

- W***hen a study includes both investigational and commercial agents, the following rules apply.***
- ***Concurrent administration: When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.***
- ***Sequential administration*:** When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm with sequential administration all expedited reporting of adverse events should follow the guidelines for the type of agent being given. For example, if the patient begins the study on the investigational agent(s), then all expedited reporting of adverse events should follow guidelines for the investigational agent(s). Once the patient begins receiving the commercial agent(s) then all expedited reporting of adverse events should follow the guidelines for commercial agent(s).

Step 2: Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov)**.** Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms.

Step 3: Grade the event using the NCI CTCAE version specified in the protocol for reporting serious adverse events

Step 4: Determine if the adverse event is Expected or an Exception to Expedited Reporting. **Expected** events are those that have been previously identified as resulting from administration of the agent and are listed in one of the following:

- The current NCI SPEER (Specific Protocol Exceptions to Expedited Reporting) for treatments using agents provided under an NCI-held IND, or an equivalent listing for treatments using agents provided under a Non-CTEP-held IND; located in Section 3.0 of the protocol.
- For treatments using commercial agents, the current CAEPR (Comprehensive Adverse Event and Potential Risks), ASAEL (Agent Specific Adverse Event List), or other list of expected toxicities located in Section 3.0 of the protocol, or the drug package insert.
- Exception to Expedited reporting located in Section 16.1f of the protocol.

An adverse event is considered **unexpected,** for expedited reporting purposes only, when either the type of event or the severity of the event is **not** listed in one of the areas outlined above.

Step 5: Determine whether the adverse event involved hospitalization or a prolongation of hospitalization (≥ 24 hours).

Step 6: Additionally, for commercial drugs, determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite. Consult the appropriate table for expedited reporting criteria for commercial agent(s).

NOTE: Any event that occurs more than 30 days after the last dose of study agent and is attributed (possible, probable, or definite) to the study agent(s) must be reported according to the instructions above and as outlined in the appropriate table in Section 16.1.

18.2 Intake Calendar

Instructions for the participant:

This is a monthly calendar on which you are to record the number of tablets/pills/capsules you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets/pills/capsules, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____

Your next appointment is: _____

Special instructions:

Month: **Year:**

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Patient Signature:_____

18.3 Potential Drug Interaction with Abiraterone Acetate

While abiraterone acetate exhibited inhibition of P450 CYPs 2C19, 2D6, and 1A2 in the in vitro enzyme interaction studies, these inhibitory effects were an order of magnitude weaker than those for classic inhibitors of 1A2 and 2D6, and 5 fold weaker than for classic inhibitors of 2C19.

There have been no reports of clinically significant drug-drug interactions involving abiraterone. Table 10 identifies medications that could potentially be affected in subjects receiving abiraterone acetate.

Drug Name	P450 Mechanism	Possible Effect
Clopidogrel	2C19 needed for prodrug activation	Decreased efficacy
Ticlopidine	2C19 needed for prodrug activation	Decreased efficacy
Metoprolol	Metabolized by 2D6	Increased drug levels
Propranolol	Metabolized by 2C19	Increased drug levels
Flecainide	Metabolized by 2D6	Increased drug levels
Propafenone	Metabolized by 2D6	Increased drug levels
Haloperidol	Metabolized by 2D6	Increased drug levels
Fluoxetine	Metabolized by 2C19	Increased drug levels
Paroxetine	Metabolized by 2C19	Increased drug levels
Sertraline	Metabolized by 2D6	Increased drug levels
Amoxapine	Metabolized by 2C19	Increased drug levels
Clomipramine	Metabolized by 2D6	Increased drug levels
Desipramine	Metabolized by 2D6	Increased drug levels
Doxepin	Metabolized by 2D6	Increased drug levels
Imipramine	Metabolized by 2D6	Increased drug levels
Nortriptyline	Metabolized by 2D6	Increased drug levels
Protriptyline	Metabolized by 2D6	Increased drug levels
Oxycodone	Metabolized by 2D6	Increased drug levels
Codeine	Prodrug activated by 2D6 to form Morphine	Decreased efficacy
Tamoxifen	Prodrug activated by 2D6	Decreased efficacy
Theophylline	Metabolized by 1A2	Increased drug levels
Cimetidine	Metabolized by 2C19	Increased drug levels

18.4 Child-Pugh Classification (CPC) of Liver Dysfunction

CPC score is calculated from the sum of the points for each CPC criteria:

CPC Classification	Level of dysfunction	Score
A	mild	5-6
B	moderate	7-9
C	severe	≥ 10

	Points		
CPC Criteria	**1**	**2**	**3**
Encephalopathy grade (see table below)	0	1 or 2	3 or 4
Ascites	Absent	Asymptomatic	Requiring intervention
Serum bilirubin, mg/dL	< 2	2 to 3	> 3
Serum albumin, g/dL	> 3.5	2.8 to 3.5	< 2.8
Prothrombin time, sec prolonged	< 4	4 to 6	> 6

Encephalopathy Grade	Definition (EEG required for Gr. 2,3,4)
0	Normal consciousness, personality, neurological exam
1	Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting
2	Lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves on EEG
3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves on EEG
4	Unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity on EEG

CPC should be calculated at baseline and prior to each treatment cycle

Informed Consent Model for S1014

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study.

Readability Statistics:	
Flesch Reading Ease	60 (targeted above 55)
Flesch-Kincaid Grade Level	8.5 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and SWOG.

  SWOG must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to SWOG. This includes consent forms for studies where all patients are registered directly through SWOG, all intergroup studies for which the registration is being credited to the (whether the registration is through the SWOG Data Operations Office or directly through the other group), as well as consent forms for studies where patients are registered via CTSU and the registration is credited to SWOG.
- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final

copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

S1014, "Abiraterone Acetate Treatment for Prostate Cancer Patients with a PSA of More Than Four Following Initial Androgen Deprivation Therapy, Phase II"

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have prostate cancer that is only partially responding to hormone therapy. Abiraterone acetate is a hormonal tablet that has been approved by the Food and Drug Administration (FDA) for more advanced prostate cancer patients who have received chemotherapy. It is considered investigational for your type of prostate cancer. We will be looking to see if abiraterone acetate improves the effectiveness of standard hormonal shots or injections. The prostate specific antigen (PSA) is a blood test used in prostate cancer screening and also to follow prostate cancer. In this study, we will follow your PSA level to help determine if abiraterone acetate is beneficial. The main goal of this study is to see if abiraterone acetate with prednisone reduces PSA.

Who is doing this study?

SWOG is sponsoring this trial. SWOG is an adult cancer clinical trials organization. SWOG is funded through the National Cancer Institute, and its network consists of about four thousand physicians at almost three hundred institutions throughout the United States. Your study doctor has met all requirements to be a member of SWOG and to perform National Cancer Institute-funded research through this Group.

Why is this study being done?

The purpose of this study is to find out what effects, good and/or bad, abiraterone acetate has on you and your prostate cancer. The effect of the prostate cancer will be measured by a blood test (prostatic specific antigen or PSA).

How many people will take part in the study?

About 38 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- History and physical exam including measuring your blood pressure
- CT scan of your abdomen and pelvis
- Bone scan
- Blood prostate specific antigen (PSA) test
- Other blood tests including those to assess your blood counts, kidney and liver function, and testosterone level.
- CT or MRI scan of the brain if your doctor feels it's necessary

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

Every 2 weeks for the first 3 months:

- Blood tests to monitor your liver

Every 4 weeks:

- History and physical exam including measuring your blood pressure
- Blood prostate specific antigen (PSA) test
- Other blood tests including those to assess your blood counts, kidney and liver function.

Every 12 weeks:

- CT scan of your abdomen and pelvis
- Bone scan

Treatment will consist of taking 4 abiraterone acetate tablets a day. Abiraterone acetate must be taken on an empty stomach. You should not eat for at least two hours before the dose of abiraterone acetate and for at least one hour after abiraterone acetate is taken. You will also take one prednisone tablet twice a day. Prednisone is a type of drug called a corticosteroid. It is a standard treatment for prostate cancer and may improve your symptoms. Prednisone also reduces some of the potential side effects associated with abiraterone acetate. Abiraterone acetate and prednisone can be taken together. Every 28 days is called a cycle. You will continue taking abiraterone acetate and prednisone as long as your disease does not get worse and side effects do not become too severe. To help keep track of the number of tablets you take and any side effects, you will need to keep a pill diary. The pill diary is called an Intake Calendar and you will need to bring it with you for your follow-up visits. Although it reflects a month's time, you should complete it daily. You need only complete one Intake Calendar for both drugs.

When I am finished taking abiraterone acetate…

After you are done taking the study drug, there will be an end of study visit. A history and physical exam with routine blood tests will be done at that time. The study personnel will continue to follow your progress approximately every 3 months for the first year after you join the study and then every 6 months thereafter for up to 3 years.

How long will I be in the study?

You will be asked to take abiraterone acetate for as long as you tolerate the treatment and it is working. After you are finished taking abiraterone acetate, the study doctor will ask you to visit the office for follow-up exams for at least up to 3 years from the time you started the study.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the abiraterone acetate can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the abiraterone acetate. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

There is a small chance of severe allergic reaction to the study drug which may be life-threatening. Abiraterone acetate may cause harm to the liver. Fewer than 10% of patients who took the study drug have had abnormal blood levels of liver enzymes. Rarely, liver failure may occur, which can lead to death. Pausing or ending the treatment helped to make liver function normal again in most of these cases. Your liver function will be checked closely with blood tests every two weeks for the first 3 months of the study and then monthly after. If your liver tests are abnormal, the dose of your study drug will be reduced or stopped. Abiraterone acetate should be used carefully in patients with a history of heart disease. Before treatment with the study drug, high blood pressure must be

controlled and low potassium must be corrected. Potassium is needed for proper function of your heart, and other important body systems.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the abiraterone acetate include those which are:

Frequent (≥ 20%) [May occur in 20 or more patients in 100]

- hypokalemia (low blood potassium, a mineral that helps regulate heart rate/function, fluid balance in the body and is needed for adequate body function)
- hypertension (high blood pressure)

Very Common (≥ 10% to <20%) [May occur between 10 and 19 patients in 100]

- edema peripheral (swelling of the legs as a result of the body keeping too much fluid)

Common (≥ 5% to <10%) [May occur between 5 to 9 patients in 100]

- dyspepsia (uncomfortable feeling in upper belly, indigestion)
- hematuria (presence of blood in the urine)
- Alanine aminotransferase increased and/or aspartate aminotransferase increased (enzymes in the blood that measure the function of the liver)
- urinary tract infection
- fractures (a break in the bone)

Less Common (≥1% to < 5% [May occur in fewer than 5 patients in 100]

- hypertriglyceridemia (high levels of fats (triglycerides) in the blood)
- angina pectoris (chest pain from the heart)
- atrial fibrillation (a fast and irregular heartbeat)
- tachycardia (rapid heartbeats)

Uncommon (< 1%) [May occur in less than 9 patients in 1000]

- adrenal insufficiency (decreased function of adrenal glands that normally help maintain blood pressure, balance minerals and fluid in your body)
- cardiac failure (heart failure, the heart is unable to supply enough blood flow to meet the body's needs.)
- arrhythmia (changes in the rhythm of the heart)
- abnormal ECG with QT prolongation (an abnormal finding on the ECG)
- bone density decreased (loss of strength of bones)
- myopathy (muscle weakness and/or muscle pain)

Unknown (frequency isn't determined since data was derived from post-marketing experience and there was no report from clinical studies)

- allergic alveolitis (swelling and irritation of the lung)

- failure of the liver to function (called acute liver failure).
- Rhabdomyolysis (breakdown of muscle tissue)
- Torsades de Pointes (rapid or irregular heart rate associated with feeling faint or lightheaded)

Possible adverse effects associated with the use of prednisone are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, mood swings, depression, exacerbation of infection (e.g., tuberculosis), exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer disease, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or other hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms of adrenal insufficiency including fever, myalgia and arthralgia.

Reproductive risks: You should not father a baby while on this study and for at least 1 week after you stop taking abiraterone acetate. Based on animal studies, abiraterone acetate may harm the unborn child. Male patients who are receiving abiraterone acetate and who have a partner of childbearing potential are advised to use a method of birth control with adequate barrier protection (e.g. condoms) as determined to be acceptable by your study doctor. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

<u>Handling abiraterone acetate tablets</u>:

This medicine may cause harm to the unborn child if given to women who are pregnant. It should not be taken by women who are breast feeding. Women who are pregnant or who may be pregnant should wear gloves if they need to touch abiraterone acetate tablets. You should notify any caregivers of this information to ensure that appropriate precautions are taken.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope abiraterone acetate will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about abiraterone acetate as a treatment for prostate cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- **Getting treatment or care for your cancer without being in a study**
- **Taking part in another study**
- **Getting no treatment**

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- SWOG
- A qualified representative of the manufacturer of abiraterone acetate, Janssen Scientific Affairs, LLC.

A description of this study will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the web site will include a summary of the results of the study. You can search this website at any time.

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Janssen Scientific Affairs, LLC will supply the abiraterone acetate at no charge while you take part in this study. Janssen Scientific Affairs, LLC will also provide funding for distribution of drug to the participating treatment sites. Janssen Scientific Affairs, LLC does not cover the cost

of getting the abiraterone acetate ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide abiraterone acetate for some reason. If this would occur, other possible options are:

- Abiraterone acetate is not currently approved by the FDA for sale in the United States for your type of prostate cancer. If the FDA approves the sale of this drug for your type of prostate cancer and if the manufacturer chooses to discontinue supplying the drug free of charge for this study, you might be able to get the abiraterone acetate directly from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no abiraterone acetate available at all, no one will be able to get more and the study would close.

If a problem with getting abiraterone acetate occurs, your study doctor will talk to you about these options.

Prednisone, goserelin acetate, leuprolide acetate, and Degarelix are commercially available and will not be provided free of charge.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your

regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*
[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to the following study. Please mark your choice.

1. **Future Contact**
   I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.
   Yes No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____