

Quality of life (QOL) during treatment with chemohormonal therapy: Analysis of E3805 Chemohormonal androgen ablation randomized trial in prostate cancer (CHAARTED)

Morgans, et al.

DOI: 10.1200/JCO.2017.75.3335

The information provided may not reflect the complete protocol or any previous amendments or modifications. As described in the Author Center (http://jco.ascopubs.org/site/ift/manuscript-guidelines.xhtml#randomized_phase_one_and_two) only specific elements of the most recent version of the protocol are requested by JCO. The protocol information is not intended to replace good clinical judgment in selecting appropriate therapy and in determining drug doses, schedules, and dose modifications. The treating physician or other health care provider is responsible for determining the best treatment for the patient. ASCO and JCO assume no responsibility for any injury or damage to persons or property arising out of the use of these protocol materials or due to any errors or omissions. Individuals seeking additional information about the protocol are encouraged to consult with the corresponding author directly.

CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer

Rev. 7/08

STUDY CHAIR: Christopher Sweeney, MBBS
 STUDY CO-CHAIR: David Jarrard, M.D.
 STUDY STATISTICIAN: Yu-Hui Chen, M.P.H., M.S.
 LABORATORY STUDIES CO-CHAIRS: Christopher Sweeney, MBBS
 Noah Hahn, M.D.
 GU COMMITTEE CHAIR: Robert DiPaola, M.D.
 PROSTATE SUBCOMMITTEE CHAIR: Michael Carducci, M.D.
 OUTCOMES SUBCOMMITTEE CO-CHAIR: David Cella, Ph.D.
 QOL CO-CHAIR: Linda Patrick-Miller, Ph.D.
 SWOG CO-CHAIR: Jorge A. Garcia, M.D.

Rev. 10/08

Version Date: July 14, 2016
NCI Update Date: June 15, 2011

Rev. 6/14

STUDY PARTICIPANTS

United States Institutions ONLY
ALLIANCE / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology Foundation, Inc
SWOG / SWOG.

This study is supported by the NCI Cancer Trials Support Unit (CTSU). Institutions not aligned with ECOG-ACRIN will participate through the CTSU mechanism (please see the index page and [Appendix IV](#) for details)

ACTIVATION DATE

July 28, 2006
 Addendum # 1 – Incorporated Prior to Activation
 Update #1 – Incorporated Prior to Activation
 Addendum # 2 – 2/07
 Update #2 – 2/07
 Addendum #3 – 7/08
 Update #3 – 7/08
 Update #4 – 10/08
 Update #5 – 4/09
 Update #6 – 8/09
 Addendum #4 – 2/10
 Update #7 – 6/11
 Update #8 – 9/11
 Addendum #5 – 12/11
 Addendum #6 – 6/14
 Addendum #7 – 4/15
 Addendum #8 – 9/16

Table of Contents

| | |
|--|----|
| Schema | 6 |
| 1. Introduction | 7 |
| 1.1 Background | 7 |
| 1.2 Rationale for selected approach and trial design | 9 |
| 1.3 Supporting Preliminary Data | 9 |
| 1.4 Rationale for Correlative Studies | 9 |
| 2. Objectives | 10 |
| 2.1 Primary Objective | 10 |
| 2.2 Secondary Objectives | 10 |
| 2.3 Tertiary Objectives | 10 |
| 3. Selection of Patients | 11 |
| 3.1 Eligibility Criteria | 11 |
| 4. Randomization Procedures | 15 |
| 4.1 Protocol Number | 16 |
| 4.2 Investigator Identification | 16 |
| 4.3 Patient Identification | 16 |
| 4.4 Eligibility Verification | 16 |
| 4.5 Stratification Factors | 16 |
| 4.6 Additional Requirements | 17 |
| 4.7 Instructions for Patients who Do Not Start Assigned Protocol Treatment | 17 |
| 5. Treatment Plan | 18 |
| 5.1 Administration Schedule | 18 |
| 5.2 Dose Modifications | 22 |
| 5.3 Adverse Event Reporting Requirements | 25 |
| 5.4 Supportive Care | 28 |
| 5.5 Duration of Therapy | 29 |
| 5.6 Duration of Follow-up | 29 |
| 6. Measurement of Effect | 30 |
| 6.1 Solid Tumor Response Criteria (RECIST) | 30 |
| 6.2 Evaluation of Patient's Best Overall Response | 32 |
| 6.3 Serological Response | 35 |
| 6.4 Endpoint Definitions | 37 |
| 6.5 Quality of Life (FACT-P) | 37 |
| 7. Study Parameters | 39 |
| 7.1 Therapeutic Parameters | 39 |
| 7.2 Biological Sample Submissions | 41 |
| 8. Drug Formulation and Procurement | 42 |
| 8.1 Docetaxel | 42 |
| 8.2 LHRH analogue (such as leuprolide, goserelin, Icave degarelix) | 45 |
| 8.3 Antiandrogens (flutamide and bicalutamide) | 45 |

| | |
|--|--------------------|
| 9. Statistical Considerations..... | 47 |
| 9.1 Introduction | 47 |
| 9.2 Endpoints | 47 |
| 9.3 Sample Size and Accrual..... | 47 |
| 9.4 Primary Objective..... | 48 |
| 9.5 Randomization and Stratification | 49 |
| 9.6 Quality of Life Analysis | 49 |
| 9.7 Gender and Ethnicity | 50 |
| 10. Sample Submissions..... | 51 |
| 10.1 Submission Summary..... | 51 |
| 10.2 Pathology Submissions..... | 51 |
| 10.3 Blood Specimen Submissions..... | 52 |
| 10.4 ECOG-ACRIN Sample Tracking System | 55 |
| 10.5 Banking..... | 55 |
| 10.6 Sample Inventory Submission Guidelines | 56 |
| 10.7 Lab Data Transfer Guidelines | 56 |
| 11. Correlative Studies..... | 57 |
| 11.1 Proteomic Study..... | 57 |
| 11.2 Germline Genetic Analysis | 58 |
| 11.3 Tumor Tissue Analysis..... | 61 |
| 12. Records to Be Kept..... | 63 |
| 13. Patient Consent and Peer Judgment | 63 |
| 14. References | 63 |
| Appendix I Informed Consent Template for Cancer Treatment Trials (English Language) [Deleted in Addendum #6] | 67 |
| Appendix II Pathology Submission Guidelines | 68 |
| Appendix III Patient Thank You Letter..... | 73 |
| Appendix IV Cancer Trials Support Unit (CTSU) Participation Procedures..... | 74 |
| Appendix V Treatment of Hypersensitivity Reactions..... | 78 |
| Appendix VI E3805 Collection and Shipping Kit Order Form..... | 79 |
| Appendix VII E3805 Clinical Supplies Shipping Form..... | 80 |

Rev. 7/08,
2/10

STUDY CHAIR

Christopher Sweeney, MBBS
Medical Oncology
Dana Farber Cancer Institute
44 Binney Street, Rm 1230
Boston, MA 02115
Phone: (617) 632-4524
Fax: (617) 632-2165

E-mail: Christopher_Sweeney@dfci.harvard.edu

STUDY CO-CHAIR

David Jarrard, M.D.
Clinical Science Center
University of Wisconsin
600 Highland Avenue
Madison, WI 53792
Tel: (608) 263-8600
Fax: (608) 263-0454

Email: jarrard@surgery.wisc.edu

Rev. 7/08

STUDY CHAIR LIAISON (SCL)

Anne E. Younger, R.N. CCRP
Indiana University Cancer Center
535 Barnhill Drive, Rm 473
Indianapolis, IN, 46202
Ph: (317) 274-0951
Fax (317) 274-4142

Email: anefoste@iupui.edu

Rev. 10/08

SWOG CO-CHAIR

Jorge A. Garcia, M.D.
Cleveland Clinic
Taussig Cancer Center
9500 Euclid Ave.
R35

Cleveland, OH 44195

Tel: (216) 444-7774

Fax: (216) 444-9474

Email: garciaj4@ccf.org

Rev. 2/07

Rev. 2/07

This study is supported by the NCI Cancer Trials Support Unit (CTSUS).

Institutions not aligned with ECOG-ACRIN will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at <https://members.ctsu.org>
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the ECOG-ACRIN. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to ECOG-ACRIN unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by ECOG-ACRIN (via postal mail). Please send query responses and delinquent data to ECOG-ACRIN and do not copy the CTSU Data Operations. ECOG-ACRIN accepts either mail or fax for responses. A cover memo indicating the study and data manager (if known) should accompany response. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the ECOG-ACRIN data center.

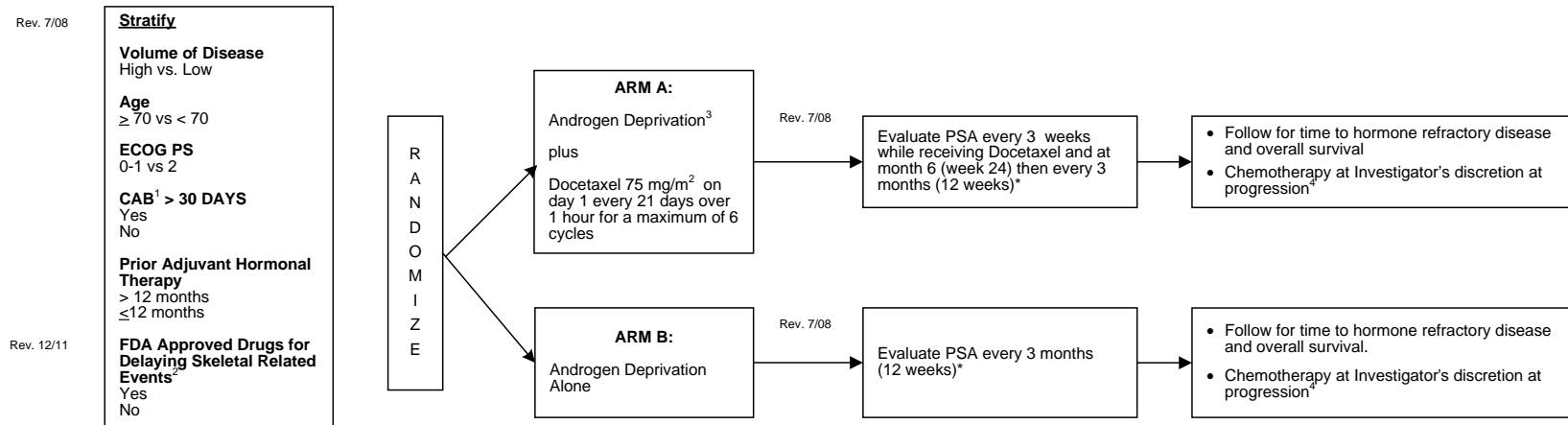
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

Rev. 2/07

| To submit site registration documents: | For patient enrollments: | Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol: |
|--|---|---|
| <p>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone - 1-888-823-5923 Fax – 215-569-0206</p> | <p>CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 8:00 AM – 8:00 PM Eastern Time, Monday – Friday (excluding holidays)</p> <p>[For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]</p> | <p>ECOG-ACRIN Operations Office – Boston, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA). Phone # 617-632-3610 Fax # 617-632-2990</p> <p>Data should be sent via postal mail (preferred), however fax is accepted.</p> <p>Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</p> |
| <p>For patient eligibility or treatment-related questions: Contact the Study PI of the Coordinating Group.</p> | | |
| <p>For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</p> | | |
| <p>The CTSU Public Web site is located at: www.ctsu.org The CTSU Registered Member Web site is located at https://members.ctsu.org</p> | | |

CTSU logistical information is located in [Appendix IV](#).

Schema



1 cycle = 21 days

Accrual goal: 780

* For Arm A patients, PSA will be checked more frequently (once every 3 weeks starting day 1 of cycle 2). Arm A patients will then have PSA checked every 3 months (12 weeks) once off-treatment. If PSA test rises > 50% of lowest level recorded since starting hormonal therapy, progression will need to be confirmed by a repeat PSA test at least 2 weeks later.

Volume of Disease:

- Visceral metastases (extranodal) AND/OR
- Bone Metastases
 - At least 4 or more bone lesions
 - One of which must be outside of the vertebral column AND pelvis.

1. **CAB:** Combined Androgen Blockade. Investigators are not obliged to use CAB but must declare whether it will be given or continued beyond testosterone surge with LHRH agonists (i.e. 30 days) when starting LHRH agonist.

2. FDA approved drug for delaying skeletal related events: Yes vs No

FDA approved for delaying skeletal related events: Doses and schedule of drugs shown to delay skeletal related events (eg zoledronic acid or denosumab every 3 to 4 week). Patients can not simultaneously enroll on CALGB90202 due to potential to confound endpoints of both studies and impacting stratification. (Please see Section 5.4.2 for Supportive Care Guidelines)

3. **Hormonal Therapy:** Combined Androgen Blockade or monotherapy as surgical or medical castration at investigator's discretion. Investigators are reminded to use combined androgen blockade for four weeks if starting LHRH agonist therapy in men with conditions that could be made worse by an initial rise in testosterone (e.g.: impending spinal cord compression.) Hormonal therapy can be commenced up to 120 days prior to randomization.

Premedication is required to decrease or prevent acute anaphylactoid reactions to docetaxel, and to decrease the severity or delay the onset of late-occurring fluid retention problems. Dexamethasone 8 mg po approximately 12, 3 and 1 hour prior to docetaxel infusion. Use of diphenhydramine is optional.

Docetaxel: 75 mg/m² of docetaxel will be given on day 1 every 21 days.

4. Type of therapy at time of hormone refractory disease is not being dictated but investigators are encouraged to treat with docetaxel every three weeks on BOTH ARMS so the effect of early versus delayed chemotherapy on overall survival can be assessed. If the investigator deems that the patient is not a suitable candidate for docetaxel chemotherapy, the reason for this decision will be recorded. All therapy for hormone refractory disease will be recorded, including anti-androgen withdrawal, second-line hormonal therapy and chemotherapy. If a patient has more than one therapy, then all therapies will be recorded. Patients will be followed until development of HRPC and for overall survival. Investigators are encouraged to continue androgen deprivation therapy at time of progression to HRPC. If however, the investigator does not feel it is in the patient's best interest, then androgen deprivation can be discontinued but must be documented in study chart.

NOTE: Docetaxel is a commercially marketed product which has been approved by the FDA for use in some cancers. However its use in patients eligible for this protocol with prostate cancer is not currently approved by the FDA. When used as directed by this protocol, docetaxel is classified as an "unapproved use of an approved agent" and, by definition, considered as an investigational agent. After patient randomization, a supply of docetaxel may be obtained. Investigators must fax a completed "E3805 Clinical Supplies Shipping Form" (Appendix VII) to the ECOG Coordinating Center, ATTN: Drug Team at 617-632-2063.

1. Introduction

1.1 Background

Rev. 7/08

Prostate cancer afflicts approximately 230,000 men per year and results in approximately 30,000 deaths (1). Although the PSA (prostate specific antigen) test has been able to diagnose prostate cancer at an earlier stage, it is unclear whether the overall mortality has decreased. The current treatment for hormone naive metastatic prostate cancer is hormone ablation either by LHRH analogue therapy or orchiectomy as monotherapy or in combination with an antiandrogen. Survival varies depending on the extent of disease at commencement of therapy. With the advent of the PSA test many patients are commenced on hormonal therapy at a very early stage and subjected to the long-term effects of androgen ablation including osteoporosis. However, if patients with an asymptomatic rising PSA after definitive local therapy are observed until they develop overt metastatic disease (i.e. evident by imaging techniques), the median time from PSA relapse to clinical progression is approximately 8 years (2). In the pre-PSA era studies relied upon bone scan and CT scans to document the presence of metastatic disease. The median overall survival for men commencing androgen ablation with clinically evident metastatic disease (i.e. not PSA only disease) is about 30 months (3). This information is derived from the meta-analysis of 27 randomized trials with 8,275 men comparing castration (medical or surgery) alone against combined androgen blockade (3). Currently, patients with overt metastases are placed solely on androgen ablation and followed until symptomatic progression. Most men are continued on androgen deprivation indefinitely. Once hormonal therapy is no longer effective, chemotherapy is employed with palliative intent and can prolong overall survival slightly. The purpose of this proposed trial is to determine whether instituting chemotherapy when starting hormonal therapy can delay the time to progression to a clinically meaningful degree without effecting quality of life in men with metastatic (extensive) disease. Patients with metastatic disease are classified into either high volume disease (i.e., metastases involving appendicular skeleton (including ribs and clavicle) with or without axial involvement and/or visceral metastases or low volume metastatic disease. Patients with high volume metastatic disease have a poorer prognosis with a median time to PSA progression of about only 10 months and median time to clinical progression (e.g. worsening bone metastases) of about 14 months. This was seen in the previous Intergroup phase III trial which accrued 1,387 patients in five years of which 75% had extensive disease (4). This was also observed in a second Intergroup trial in the same population (5). In contrast patients with low volume metastatic disease have a 22 month median time to PSA progression with androgen ablation alone and median time to clinical progression of more than three years. The short time to clinical progression also results in men with high volume disease having a median overall survival of only 24 months compared to about four years for patients with minimal disease. Clearly, men with extensive disease are in urgent need of more effective therapies.

Until recently no therapy for hormone refractory prostate cancer (HRPC) had been shown to confer a survival advantage although numerous approaches improved the quality of life of these patients. These include radio-pharmaceuticals (strontium, samarium) (6), suramin (7), and low dose corticosteroids (8). Mitoxantrone combined with a low dose corticosteroid was

the standard treatment in the 1990's based on two randomized studies that compared this combination to the corticosteroid alone (9, 10). In both studies, there was a palliative benefit as evidenced by a decrease in pain or opiate requirements but no survival benefit for patients who received mitoxantrone.

Recently, two large phase III trials showed a survival benefit for men with hormone refractory prostate cancer treated with a docetaxel-based regimen (11, 12). One is the SWOG 9916 trial of docetaxel plus estramustine versus mitoxantrone plus prednisone. Docetaxel was dosed at 60 mg/m² every 3 weeks plus 5 days of oral estramustine. The lower docetaxel dose was to minimize toxicities seen at 70 mg/m². Patients were escalated from 60 mg/m² to 70 mg/m² if no grade 3 or 4 toxicities occurred in the first cycle. The other is a multinational trial (TAX327) of single agent docetaxel given either weekly (30 mg/m²) or every three weeks (75 mg/m²) versus mitoxantrone plus prednisone. In the latter study prednisone 5 mg twice per day was dosed continuously. In both studies every three week docetaxel was more effective in terms of serological response and overall survival. The mitoxantrone plus prednisone arm in the SWOG study had a PSA response of 27% versus 50% with every three week docetaxel plus estramustine (p<0.001) and the corresponding result in the TAX327 trial for the mitoxantrone plus prednisone arm was 32% versus 45% in the every 3 week docetaxel arm (P<0.001). The overall survival also favored docetaxel based therapy with the median survival for mitoxantrone plus prednisone versus every three week docetaxel being 16 versus 18 months in the SWOG study (p=0.008) and 16.5 versus 18.9 months (p=0.009) in TAX327. Docetaxel every three weeks without estramustine, is therefore the optimal regimen. The weekly regimen did not provide any significant benefits.

Rev. 7/08

This trial aims to evaluate whether early use of active chemotherapy (docetaxel) in men with metastatic disease in combination with hormonal therapy can delay the time to development of progression/hormone refractory disease and ultimately increase overall survival. Given the fact patients are going to be starting hormonal therapy (androgen ablation) daily prednisone will not be given with the docetaxel in this protocol and will thus minimize the toxicity of chronic low dose steroid exposure. This is expected to make the regimen better tolerated for the 18 weeks it is planned to be administered and will remove this as a confounding variable.

Rev. 7/08

A theory in support of why early chemotherapy may be more beneficial when starting hormonal therapy is that chemotherapy may be more effective on small volume disease that has not been eradicated by androgen deprivation. This has the potential to delay the time to progression and hence prolong disease control. An argument against combining chemotherapy with hormonal therapy is that the androgen deprivation takes the cells out of cycle and may cause the chemotherapy to be less effective. A randomized phase III trial is required to answer this question. A quality of life analysis will be incorporated to determine whether the postulated clinically meaningful increase in disease control is not associated with an overall decrement in quality of life. A clinically significant increase in disease control is considered to be an increase in the median overall survival from 24 to 32 months in men with high volume metastatic disease and 48 to 62 months with low volume metastatic prostate cancer. This is considered to be of a magnitude large enough that would alter the current standard of care if quality of life was not impaired.

1.2 Rationale for selected approach and trial design

In summary, docetaxel based chemotherapy has shown significant activity in hormone refractory prostate cancer. The therapy to be taken forward to the phase III trial of patients in patients STARTING hormonal therapy has been chosen based on the results of the phase III trials in the hormone refractory setting. A randomized phase III trial is required to definitively answer the question of whether early chemotherapy plus androgen ablation can significantly increase the duration of cancer control versus androgen ablation alone.

1.3 Supporting Preliminary Data

To date, only one trial has been completed and analyzed addressing the question of chemohormonal therapy as primary therapy for metastatic hormone sensitive prostate cancer. The MDACC group, lead by Dr. Millikan compared androgen deprivation to androgen deprivation with ketoconazole, adriamycin, vinblastine and estramustine (KAVE). It is reported that the median time to PSA progression in patients with high volume metastases was 10 months in the 64 patients with androgen deprivation alone and 19 months in those with chemohormonal therapy. For the 50 patients with low volume metastases, there was no improvement in time to PSA progression as it was 22 months in both arms with about 24 patients per arm. At the time of this analysis there was no improvement in overall survival in either group (Personal Communication: Randall Millikan).

From this study we at least know that two relatively ineffective chemotherapy agents (adriamycin and vinblastine) prolonged time to PSA progression in patients with high volume metastatic burden. Docetaxel holds even more promise based on the data showing improvement over mitoxantrone plus prednisone in HRPC. Another theoretical advantage for using docetaxel is that it can abrogate BCL-2's anti-apoptotic properties (13) which has been shown to be involved in the emergence of androgen insensitive clones (14-18). It has also been reported that retreatment after a "drug holiday" with docetaxel, if no progression on docetaxel, can result in significant responses (19). Thus, retreatment with docetaxel at the time of progression has the possibility of compounding its own clinical benefit by adding to the total time of disease control when re-instituted when a patient is hormone refractory.

Rev. 7/08

1.4 Rationale for Correlative Studies

In addition to asking the question of whether chemotherapy at the time of starting hormonal therapy prolongs survival, this clinical trial provides a unique opportunity to collect specimens (tumor specimens and blood) that will be annotated with clinical information. The intent of the genetic studies will be to identify genes in the patients' germline DNA and/or tumor that predict response and toxicity. The sequential blood analyses will allow for proteins to be studied longitudinally and thus further facilitate potential biomarker discovery.

Rev. 7/08

2. Objectives

2.1 Primary Objective

- 2.1.1 To evaluate the ability of early chemotherapy to improve overall survival in men commencing androgen deprivation for metastatic prostate cancer.

2.2 Secondary Objectives

- 2.2.1 To determine whether early chemotherapy can increase the time to clinical progression (radiographic or symptomatic deterioration due to disease) over hormonal therapy alone.
- 2.2.2 To determine whether early chemotherapy can increase the time to development of hormone refractory disease over hormonal therapy alone.
- 2.2.3 To determine whether early chemotherapy can increase time to serological progression over hormonal therapy alone.
- 2.2.4 To determine rates of biochemical response at 6 months and 12 months in the chemohormonal arm versus the hormonal therapy alone arm.
- 2.2.5 To determine the frequency of adverse events and the tolerability of chemotherapy combined with hormonal therapy versus hormonal therapy alone.
- 2.2.6 To determine whether the postulated clinically meaningful increase in disease control is associated with an alteration in overall quality of life using the Functional Assessment of Cancer Therapy–Prostate questionnaire (FACT-P self-administered).
- 2.2.7 To determine the ability of PSA changes to be a surrogate for clinical benefit from therapy and overall survival.

2.3 Tertiary Objectives

- 2.3.1 To determine if there are proteins differentially translated from the genome in hormone sensitive prostate cancer, prostate cancer that has responded to hormonal therapy and hormone refractory prostate cancer.
- 2.3.2 To determine the frequency of constitutive polymorphisms of enzymes involved in steroid metabolism and other carcinogenic processes.
- 2.3.3 To determine if the amount and frequency of certain carcinogenic proteins in prostate cancer tissue, such as CXCR4 and Manganese Superoxide Dismutase, can be correlated with a poor prognosis.

Rev. 7/08

Rev. 7/08

3. Selection of Patients

Each of the criteria in the following section must be met in order for a patient to be considered eligible for this study. Use the spaces provided to confirm a patient's eligibility. For each patient, this section should be photocopied, completed and maintained in the patient's chart.

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 four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

NOTE: All questions regarding eligibility should be directed to the ECOG-ACRIN Operations Office – Boston at (617) 632-3610.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to randomization by the treating physician.

3.1 Eligibility Criteria

Rev. 2/07
Rev. 7/08

_____ 3.1.1 Patients must have histologically or cytologically confirmed prostate cancer. Patients may have begun hormonal therapy but it must not have commenced more than 120 days prior to randomization.

Rev. 7/08

Rarely pathology is not available but if clinical situation confirms prostate cancer (such as response to androgen ablation) pathology is not required and patient can be enrolled after discussed with study chair.

Rev. 2/07, 7/08

_____ 3.1.2 Patients must have metastatic disease and will be stratified by presence of high volume or low volume disease. Low volume disease is defined as any metastatic disease that is not extensive. High volume disease is defined as:

Rev. 6/14

- Visceral Metastases (extranodal)
AND/OR

Rev. 6/14

- Bone Metastases

Rev. 6/14

- At least 4 or more bone lesions
- One of which must be outside of the vertebral column AND pelvis.

NOTE: Radiological studies identifying measurable or non-measurable disease must be obtained according to the following criteria:

- If androgen deprivation therapy has not commenced:
 - Scans must be obtained within 6 weeks of randomization
- If androgen deprivation has commenced prior to randomization:

- Rev. 7/08
- Scans must be obtained within 6 weeks prior to the start of androgen deprivation therapy.
- Rev. 7/08
- If all required imaging had not been completed prior to starting androgen deprivation, then any additional scans must be obtained after starting androgen deprivation but prior to randomization. (It is assumed the scans of patients with high volume disease would not normalize in less than 120 days to the point a patient would go from “high volume” to “low volume.”)
- Rev. 7/08
12/11
- _____ 3.1.3 Patients are not eligible if the PSA has risen and met criteria for progression as defined in Section [6.3.1](#) from its lowest point between the beginning of androgen deprivation therapy and the date of randomization.
- _____ 3.1.4 Patients must have adequate organ function within 4 weeks prior to randomization and evidenced by:
- _____ 3.1.4.1 Absolute Neutrophil Count $\geq 1500/\text{mm}^3$
ANC: _____ Date of test: _____
- _____ 3.1.4.2 Platelet count $\geq 100,000/\text{mm}^3$
Platelet count: _____ Date of test: _____
- _____ 3.1.4.3 Total bilirubin \leq ULN
Total bilirubin: _____ Date of test: _____
- Rev. 7/08
ULN: _____ Date of test: _____
- Rev. 7/08
- _____ 3.1.4.4 ALT ≤ 2.5 X upper limit of normal
ALT: _____ Date of test: _____
ULN: _____ Date of test: _____
- Rev. 7/08
- _____ 3.1.4.5 Creatinine clearance of ≥ 30 mL/min. Creatinine clearance (CrCl) should be calculated at screening using the Cockcroft-Gault formula:
Creatinine clearance for males (mL/min) = $(140 - \text{age})(\text{body weight in kg})/[72 \times (\text{serum creatinine in mg/dl})]$
Creatinine clearance: _____ Date of test: _____
- Rev. 7/08
- _____ 3.1.4.6 PT, INR ≤ 1.5 x ULN (except if on therapeutic anti-coagulation in which case the patient can be enrolled if stable and anti-coagulation levels are appropriate for their condition per good clinical practice).
PT: _____ Date of test: _____
INR: _____ Date of test: _____
ULN: _____ Date of test: _____

- Rev. 7/08 _____ 3.1.4.7 PTT \leq 1.5 x ULN (except if on therapeutic anti-coagulation in which case the patient can be enrolled if stable and anti-coagulation levels are appropriate for their condition per good clinical practice).
PTT: _____ Date of test: _____
ULN: _____ Date of test: _____
- Rev. 7/08 _____ 3.1.4.8 Patients can enter the study if on therapeutic anti-coagulation.
NOTE: All values must be obtained within 4 weeks prior to beginning protocol therapy.
- Rev. 7/08 _____ 3.1.5 If a patient has had major surgery, the patient must be longer than 4 weeks post major surgery and recovered from all toxicity prior to randomization.
- Rev. 7/08 _____ 3.1.6 Patients must have discontinued hormonal therapy in the adjuvant and/or neoadjuvant setting 12 months prior to beginning protocol therapy, AND must not have exceeded 24 months of therapy AND have shown to have no evidence of disease (PSA < 0.1 ng/dL after prostatectomy plus hormonal therapy and < 0.5 ng/dL and not have doubled above nadir after radiation therapy plus hormonal therapy) at least 12 months after completing adjuvant or neoadjuvant hormonal therapy. Patients with prior chemotherapy in the adjuvant or neoadjuvant setting are ineligible. The last depot injection must have expired by the time the 24 month mark was reached.

(e.g., patient completed 24 months of adjuvant therapy with 8 three month depot LHRH agonists injections – last dose given 8/03 – 24 months completed 11/03. Patient is eligible if no evidence of disease at or after 11/04 and commenced hormonal therapy for metastatic disease on or after 11/04).
- Rev. 2/10
- Rev. 7/08 _____ 3.1.7 Patients must have ECOG performance status of 0- 2. (NOTE: Patients with PS 2 are only eligible if the decline in PS is due to metastatic prostate cancer).
- _____ 3.1.8 Patients must be at least 18 years of age.
- Rev. 12/11 _____ 3.1.9 Patients must not have participated in another clinical trial within 30 days prior to randomization. Patients may participate in non-therapeutic trials. Patients can not simultaneously enroll on CALGB 90202 due to the potential to confound endpoints of both studies and impact the stratification.
- _____ 3.1.10 Patients must not have prior history of malignancy in the past 5 years with the exception of basal cell and squamous cell carcinoma of the skin. Other malignancies that are considered to have a low potential to progress (eg: grade 2, T1A TCC) may be enrolled if approved by study chair.
- Rev. 7/08
- _____ 3.1.11 Peripheral neuropathy must be \leq grade 1.

- _____ 3.1.12 Patients with a history of severe hypersensitivity reaction to Docetaxel® or other drugs formulated with polysorbate 80 must be excluded.
- _____ 3.1.13 No active cardiac disease defined as active angina, symptomatic congestive heart failure, or myocardial infarction within previous six months.
- _____ 3.1.14 Patients may be enrolled if they have had prior palliative radiation therapy. However, this has to have been commenced within 30 days of starting androgen deprivation.
- _____ 3.1.15 Patients with prior hormone therapy in the metastatic setting are not eligible.

Rev. 7/08

4. Randomization Procedures

Submitting Regulatory Documents

Before an ECOG-ACRIN Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX: (215) 569-0206

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.
2. Copy of IRB Informed Consent Document.

NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. A. CTSU IRB Certification Form.
Or
B. HHS 310 Form.
Or
C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- Indicate all sites approved for the protocol under an assurance number.
- OHRP assurance number of reviewing IRB
- Full protocol title and number
- Version Date
- Type of review (full board vs. expedited)
- Date of review.
- Signature of IRB official

The CTSU encourages you to link to the following RSS2.0 webpage so that more information on RSS2.0 as well as the submission forms can be accessed http://www.ctsu.org/rss2_page.asp. If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail CTSUContact@westat.com.

Patients must not start protocol treatment prior to randomization.

Treatment should start within seven working days after randomization.

NOTE: Please refer to [Appendix IV](#) for CTSU registration guidelines.

Institutions may register eligible patients to this study via the ECOG webpage 24 hours a day, 7 days a week, using the Web-based Patient Registration Program

Rev. 6/14

Rev. 7/08

(<https://webreg.ecog.org>). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG-ACRIN Operations Office – Boston at (617) 632-2022, Monday through Friday 9:00am – 5:00pm Eastern Time. Please note that a password is required to use this program. The following information will be requested:

4.1 Protocol Number

4.2 Investigator Identification

4.2.1 Institution and affiliate name

4.2.2 Investigator's name

4.3 Patient Identification

4.3.1 Patient's initials and chart number

4.3.2 Patient's Social Security number

4.3.3 Patient demographics

4.3.3.1 Sex

4.3.3.2 Birth date (mm/yyyy)

4.3.3.3 Race

4.3.3.4 Ethnicity

4.3.3.5 Nine-digit ZIP code

4.3.3.6 Method of payment

4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG-ACRIN Operations Office – Boston.

4.5 Stratification Factors

4.5.1 Age

4.5.1.1 ≥ 70

4.5.1.2 < 70

4.5.2 ECOG Performance Status

4.5.2.1 PS 0-1

4.5.2.2 PS 2

4.5.3 CAB > 30 Days

4.5.3.1 Yes

4.5.3.2 No

4.5.4 Prior Adjuvant Hormonal Therapy

4.5.4.1 > 12 months

4.5.4.2 ≤ 12 months

Rev. 12/11

4.5.5 FDA Approved Drugs for Delaying Skeletal Related Events

4.5.5.1 Yes

4.5.5.2 No

Rev. 7/08

4.5.6 Volume of Disease

4.5.6.1 High

4.5.6.2 Low

4.6 Additional Requirements

4.6.1 Patients must provide a signed and dated, written informed consent form.

4.6.2 Correlative samples should be submitted for analysis as outlined in Sections [10](#) and [11](#).

Rev. 7/08

NOTE: ECOG-ACRIN requires that all biological samples submitted from patients participating in this trial be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See Section [10.4](#).

4.7 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E3805 Forms Packet. Document the reason for not starting protocol treatment on the Off Treatment Form. Also report the date and type of the first non-protocol treatment that the patient receives.

5. Treatment Plan

5.1 Administration Schedule

5.1.1 Arm A: Androgen Deprivation plus Docetaxel

5.1.1.1 Androgen Deprivation Therapy

Options for androgen-deprivation (i.e., hormone ablation) therapy include the following:

- LHRH agonist or antagonist therapy
- Surgical castration

Rev. 2/10

NOTE: Patients can be randomized to the study within 7 working days before beginning docetaxel and may begin androgen-deprivation therapy up to 120 days before randomization.

Rev. 7/08

Use of combined androgen blockade (medical or surgical castration combined with antiandrogen treatment) is to be instituted at the investigator's discretion.

Antiandrogens (e.g., bicalutamide or flutamide) may be used in addition to androgen-deprivation therapy, but may not be used as the sole hormonal therapy. Anti-androgens combined with 5-alpha reductase inhibitors are also not allowed as sole therapy. An investigator may administer this class of drug as a single agent ≤ 28 days before medical castration to cover the testosterone surge associated with LHRH agonists. *The 120-day window of androgen-deprivation or hormonal therapy starts with commencement of either the antiandrogen or LHRH therapy.* An agent such as ketoconazole may be used in addition if urgent control of cancer is required but must be discontinued prior to randomization.

Rev. 7/08, 12/11
Rev. 7/08

Rev. 12/11

5.1.1.2 Docetaxel

75 mg/m² of docetaxel will be given on day 1 every 21 days over one hour for up to 6 cycles (1 cycle = 21 days).

Rev. 7/08

NOTE: Docetaxel is a commercially marketed product which has been approved by the FDA for use in some cancers. However its use in patients eligible for this protocol with prostate cancer is not currently approved by the FDA. When used as directed by this protocol, docetaxel is classified as an "unapproved use of an approved agent" and, by definition, considered as an investigational agent. After patient randomization, a supply of docetaxel may be obtained. Investigators must fax a completed "E3805 Clinical Supplies Shipping Form" ([Appendix VII](#)) to the ECOG-ACRIN Operations

Office – Boston, ATTN: Drug Team at 617-632-2063.

5.1.1.3 Premedication for Docetaxel

Premedication is required to decrease or prevent acute anaphylactoid reactions to docetaxel, and to decrease the severity or delay the onset of late-occurring fluid retention problems. Dexamethasone 8 mg po approximately 12, 3 and 1 hour prior to docetaxel infusion. Use of diphenhydramine is optional.

5.1.1.4 Calcium Carbonate

Patients will receive concomitant treatment with calcium carbonate at a dose of at least 500 mg orally per day every evening (any product with amount stated on the bottle and verified by investigator, e.g., TumsTM). Calcium is best absorbed when taken with meals.

5.1.1.5 Vitamin D

Patients will receive concomitant treatment with vitamin D by administration of any multivitamin containing at least 400 IU of vitamin D (any product with amount stated on the bottle and verified by investigator).

Rev. 12/11

For guidance on use of drugs to prevent skeletal related events, please see Section [5.4.2](#) (Supportive Care).

At the time of hormone refractory disease, investigators are encouraged to treat with docetaxel therapy every three weeks ON BOTH ARMS so the effect of early versus delayed chemotherapy on overall survival can be assessed. If the investigator deems that the patient is not a suitable candidate for docetaxel chemotherapy, the reason for this decision will be recorded. All therapy for hormone refractory disease will be recorded including anti-androgen withdrawal, second-line hormonal therapy and chemotherapy. If a patient has more than one therapy, then all therapies will be recorded. Patients will be followed until development of HRPC and for overall survival. Investigators are encouraged to continue androgen deprivation therapy at time of progression to HRPC. If however, the investigator does not feel it is in the patient's best interest, then androgen deprivation can be discontinued but must be documented in the study chart.

Rev. 7/08

Rev. 7/08

5.1.2 Arm B: Androgen Deprivation Alone

5.1.2.1 Androgen Deprivation Therapy

Options for androgen-deprivation (i.e., hormone ablation) therapy include the following:

- LHRH agonist or antagonist therapy
- Surgical castration

Rev. 7/08

NOTE: Patients may begin androgen-deprivation therapy up to 120 days before randomization.

Use of combined androgen blockade (medical or surgical castration combined with antiandrogen treatment) is to be instituted at the investigator's discretion.

Antiandrogens (e.g., bicalutamide or flutamide) may be used in addition to androgen-deprivation therapy, but may not be used as the sole hormonal therapy. Anti-androgens combined with 5-alpha reductase inhibitors are also not allowed as sole therapy. An investigator may administer this class of drug as a single agent \leq 28 days before medical castration to cover the testosterone surge associated with LHRH agonists. *The 120-day window of androgen-deprivation or hormonal therapy starts with commencement of either the antiandrogen or LHRH therapy.* An agent such as ketoconazole may be used in addition if urgent control of cancer is required but must be discontinued prior to randomization.

Rev. 12/11
Rev. 7/08

Rev. 7/08

Rev. 12/11

5.1.2.2 Calcium Carbonate

Patients will receive concomitant treatment with calcium carbonate at a dose of at least 500 mg orally per day every evening (any product with amount stated on the bottle and verified by investigator, e.g., TumsTM). Calcium is best absorbed when taken with meals.

5.1.2.3 Vitamin D

Patients will receive concomitant treatment with vitamin D by administration of any multivitamin containing at least 400 IU of vitamin D (any product with amount stated on the bottle and verified by investigator).

Rev. 12/11

For guidance on use of drugs to prevent skeletal related events, please see Section [5.4.2](#) (Supportive Care).

At the time of hormone refractory disease, investigators are encouraged to treat with docetaxel therapy every three weeks ON BOTH ARMS so the effect of early versus delayed chemotherapy on overall survival can be assessed. If the investigator deems that the patient is not a suitable candidate for docetaxel chemotherapy, the reason for this decision will be recorded. All therapy for hormone refractory disease will be recorded including anti-androgen withdrawal, second-line hormonal therapy and chemotherapy. If a patient has more than one therapy, then all therapies will be recorded. Patients will be followed until development of HRPC and for overall survival. Investigators are encouraged to continue androgen deprivation therapy at time of progression to HRPC. If however, the investigator does not feel it is in the patient's

Rev. 7/08

best interest, then androgen deprivation can be discontinued but must be documented in the study chart.

Rev. 2/07

5.1.3

For Arms A and B: Quality of Life (QOL)

Quality of Life will be measured at the following timepoints:

Rev. 12/11

- Baseline (within 1 week prior to docetaxel therapy on Arm A and within 2 weeks of randomization)
- Week 12 (3 months)
- Week 24 (6 months)
- Week 36 (9 months)
- Week 48 (12 months)

Administration of the four part questionnaire (FACT-P, FACIT-F Fatigue Subscale, FACT-Taxane Subscale and the Brief Pain inventory) will allow us to examine overall QOL, as well as specific treatment-associated and disease-associated changes in QOL. The questionnaire should be administered to patients by staff during visits. Differences between pre-treatment and subsequent scores will be analyzed using appropriate statistical tests.

- 5.1.3.1 The questionnaire must be administered at the timepoints listed above unless the patient refuses. The patient should be instructed to respond to the questionnaire in terms of his experience during the time frame specified on each questionnaire.
- 5.1.3.2 The patient should be asked to read the instructions at the beginning of each questionnaire and complete all of the items. It is permissible to assist the patient with the completion of the questionnaire as long as the staff person does not influence the patient's responses.
- 5.1.3.3 The questionnaire must be reviewed by the protocol nurse or research coordinator as soon as the patient completes them to ensure all items were marked appropriately. If more than one answer was marked, the patient should be asked to choose the answer which best reflects how he is feeling. If a question was not answered, the patient should be asked if he would like to answer it. The patient should always have the option to refuse. If the patient refuses, it should be indicated on the questionnaire that he declined to answer the item.
- 5.1.3.4 Completed questionnaires must be returned to the ECOG-ACRIN Operations Office – Boston. If a questionnaire cannot be completed by the patient, the reason should be noted on the Assessment Compliance Form and the form should be returned to the ECOG-ACRIN Operations Office – Boston.
- 5.1.3.5 If a patient misses an appointment on the scheduled date, the questionnaire may be completed by telephone on the

appointed date or at the time the appointment is rescheduled. If the missed date is on a treatments date, the QOL assessment will be done when the patient comes for the rescheduled treatment.

- 5.1.3.6 If a patient cannot complete the questionnaire because he is too sick, this should be documented on the Assessment Compliance Form.

5.2 Dose Modifications

There will be no dose modifications for androgen deprivation. Intermittent hormonal therapy is not allowed.

For docetaxel, no more than two dose modifications should be allowed for any patient. If a patient requires a third reduction of docetaxel, they will be followed every 12 weeks and treated with androgen deprivation alone. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. **All toxicities should be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE version 4.0 is identified and located on the CTEP website at <http://ctep.cancer.gov>. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.**

Dose adjustments for toxicity should be made according to the guidelines that follow. If a dose is reduced due to toxicity the dose will not be re-escalated back to starting level. Treatment may be delayed no more than three weeks to allow recovery from toxicity. If treatment must be delayed longer than three weeks from scheduled day of dosing, patient will be treated with androgen deprivation alone.

| Dose Level | Docetaxel (mg/m ²) |
|------------|--------------------------------|
| Level 0 | 75 mg/m ² |
| Level - 1 | 65 mg/m ² |
| Level - 2 | 55 mg/m ² |

5.2.1 Dose Modifications for Myelosuppression

Dose modifications to be made based on granulocyte and/or platelet count drawn prior to planned treatment (can be done day prior to planned dose):

| Docetaxel | Granulocytes/mm ³ Day 1 of treatment | Platelet/mm ³ Day 1 of treatment |
|---------------------------|--|--|
| No change | > 1,500 ^ψ | or > 100,000 |
| Reduce one dose level # | 1,000 to 1,499 | or 75,000 to 99,999 |
| Delay dosing one week * + | <1000 | or < 75,000 |

NOTE: If a dose reduction is made, maintain the lower dose for all subsequent cycles

Rev. 9/11

Rev. 7/08, 12/11

- # A need for three dose reductions will require that the patient discontinue docetaxel and continue on androgen ablation alone.
- * If planned day 1 dose must be delayed for three consecutive weeks, discontinue docetaxel and continue on androgen ablation alone.
- + If a dose is held due to myelosuppression, the patient will be retreated with a one level dose reduction once granulocyte count has recovered to at least 1,500/mm³ and platelet count has recovered to at least 100,000/mm³.
- ψ Management of prolonged grade 4 neutropenia and neutropenic fever- In order to maximize dose intensity, patients with afebrile Grade 4 neutropenia ≥ 7 days or Grade ≥ 3 neutropenia associated with fever (one reading of oral temperature > 38.5°C, or three readings of oral temperature >38.0°C in a 24-hour period) should be retreated after recovery to an absolute neutrophil count to 1,500 granulocytes/mm³ but with a one level dose reduction. The fever must have resolved and if an infection is identified, it must be adequately treated and have clinically resolved before restarting therapy. If prior bacteremia, blood cultures must be negative on recheck. Patient can continue with chemotherapy dosing while on antibiotics.

Rev. 7/08

Rev. 12/11

Use of growth factors is not required as the dose and scheduled dose not meet ASCO guidelines. If however, the investigator considers it in patients best interest growth factors can be used per investigator discretion.

5.2.2 Dose Modification for Hepatic Dysfunction

Rev. 7/08

ALT and Bilirubin will be evaluated pre-study and Day 1 (may be evaluated within 24 hours of day 1) of cycles 1-6:

Patients who develop abnormal liver function tests for any reason while on the study will have the following dose reductions:

Dose Modifications for Abnormal Liver Function

| Bilirubin | | ALT/ SGPT | Action |
|-----------|-----|-----------|--|
| > ULN | or | > 5 x ULN | Wait ≤ 3 weeks. If recovered*, reduce docetaxel dose by one dose level. If not, discontinue docetaxel. |
| ≤ ULN | and | > 3 x ULN | Treat without delay but reduce docetaxel dose by one dose level |

Rev. 7/08

* Recovery is < 3X ULN for ALT/SGPT and WNL for bilirubin. Dose modifications are based on SGPT alone due to confounding effect of bone disease on SGOT levels.

5.2.3 Dose Modification for Stomatitis

Rev. 12/11

If stomatitis ≥ grade 2 is present on day 1 of any cycle, docetaxel should be held until stomatitis has resolved. If Grade 3/4 stomatitis occurs at any time, the dose of docetaxel will be reduced one dose level for all subsequent doses. If a second Grade 3/4 stomatitis event is incurred, docetaxel will be reduced one more dose level. If a third Grade 3/4 stomatitis event occurs, the patient will be taken off study.

- 5.2.4 Dose Modification for Peripheral Neuropathy
- If \geq Grade 3, the patient will discontinue docetaxel.
- If Grade 2, the Docetaxel will be held and the patient should be retreated upon recovery to a \leq Grade 1 toxicity with a dose reduction of Docetaxel by one level.
- If Grade 2 or greater neurotoxicity persists for more than 3 weeks, the patient will discontinue docetaxel.
- 5.2.5 Hypersensitivity Reactions for Docetaxel
- See [Appendix V](#) for treatment of hypersensitivity reactions. Treatment should be discontinued for Grade 4 hypersensitivity reactions. There are no dose reductions for hypersensitivity reactions.
- Grade 4 Hypersensitivity is defined as a reaction that is life threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion.
- Patients with two episodes of Grade 3 Hypersensitivity reactions or one Grade 4 Hypersensitivity reaction are to discontinue docetaxel.
- 5.2.6 Diarrhea
- If patients experience $>$ grade 2 diarrhea and concurrent grade 3 or 4 neutropenia, hold Docetaxel until ANC $>$ 1000/mm³ and diarrhea \leq grade 2.
- If patients experience significant diarrhea ($>$ 3 loose stools/24hrs over baseline), they should be treated prophylactically in subsequent cycles with loperamide or diphenoxylate. If patient experiences $>$ grade 2 diarrhea despite prophylaxis, Docetaxel should be reduced one dose level. If patients experience $>$ grade 2 diarrhea despite prophylaxis AND dose reduction, they should discontinue docetaxel.
- 5.2.7 Delay of Therapy:
- If docetaxel has to be delayed for more than 3 weeks from planned day of dosing because of any toxicity, then the patient is to be treated with androgen deprivation alone.
- 5.2.8 Other Toxic Effects Thought to be related to docetaxel:
- If toxicities \leq Grade 2, manage the subject symptomatically if possible, and retreat without dose reduction.
- If toxicities \geq Grade 3 and clinically significant (not mentioned above), docetaxel should be withheld (except for anemia as patients can be transfused) until resolution to \leq Grade 1 or baseline and patients treated with a one dose level reduction.

Rev. 6/14

5.3 Adverse Event Reporting Requirements

5.3.1 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 (please refer to the E3805 Forms Packet for the list of forms with directions for routine adverse event reporting). Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

5.3.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

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.

Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: *Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.* 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. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: *Grade the event using the NCI CTCAE.*

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event.* *Expected* events are those that have been previously identified as resulting from administration of the agent. 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:

Rev. 6/14

- **Arm A and B** – the drug package insert or protocol

Step 5: Review Section [5.3.6](#) for E3805 and/or ECOG-ACRIN specific requirements for expedited reporting of specific adverse events that require special monitoring.

NOTE: For general questions regarding expedited reporting requirements, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497.

Rev. 7/08, 9/16

5.3.3 Reporting methods

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). The CTEP's guidelines for CTEP-AERS can be found at <http://ctep.cancer.gov>. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at <http://ctep.cancer.gov>.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610)
- the FDA (1-800-FDA-1088)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178) in the same timeframe.

CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.3.4 When to report an event in an expedited manner

When an adverse event requires expedited reporting, submit a full CTEP-AERS report within the timeframes outlined in Section [5.3.6](#).

NOTE: Adverse events that meet the reporting requirements in Section [5.3.6](#) and occur within 30 days of the last dose of protocol treatment must be reported on an expedited adverse event report form (using CTEP-AERS). For any adverse events that occur more than 30 days after the last dose of treatment, only those that have an attribution of possibly, probably, or definitely AND meet the reporting requirements in Section [5.3.6](#) must be reported on an expedited adverse event report form (using CTEP-AERS).

5.3.5 Other recipients of adverse event reports

ECOG-ACRIN will forward CTEP-AERS reports to the appropriate regulatory agencies and pharmaceutical company, if applicable.

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

5.3.6 Expedited reporting for commercial agents

Commercial reporting requirements are provided below. The commercial agent used in arms A and B of this study is Docetaxel.

Rev. 7/08

| Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only – Arms A and B | | | | | |
|--|-----------------|----------|----------------------|-----------------|---|
| Attribution | Grade 4 | | Grade 5 ^a | | ECOG-ACRIN and Protocol-Specific Requirements |
| | Unexpected | Expected | Unexpected | Expected | |
| Unrelated or Unlikely | | | 7 calendar days | 7 calendar days | See footnote (b) for special requirements. |
| Possible, Probable, Definite | 7 calendar days | | 7 calendar days | 7 calendar days | |
| 7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event. | | | | | |
| <p>a This includes all deaths within 30 days of the last dose of treatment regardless of attribution. NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.</p> <p>b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial: Serious Events: Any event following treatment that results in <u>persistent or significant disabilities/incapacities, congenital anomalies, or birth defects</u> must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the NCI Medical Help Desk at 301-897-7497.</p> | | | | | |

Rev. 12/11

5.3.7 Reporting secondary Primary Cancers

All cases of second primary cancers (defined as a cancer caused by any treatment for a previous malignancy) including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur in patients on NCI-sponsored trials during or following their chemotherapy for cancer must be reported to ECOG-ACRIN. Report the following information following a diagnosis of a secondary primary cancer:

- **For secondary primary cancers that are NOT related to any anti-cancer treatment (including the treatment on this protocol):**
 1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at
 ECOG-ACRIN Operations Office – Boston
 FSTRF
 900 Commonwealth Avenue
 Boston, MA 02215

2. Submit a copy of the pathology report to ECOG-ACRIN confirming the diagnosis.
3. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN.
- **For secondary primary cancers that ARE related to any anti-cancer treatment (including the treatment on this protocol):**
 1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at
ECOG-ACRIN Operations Office – Boston
FSTRF
900 Commonwealth Avenue
Boston, MA 02215
 2. Report the diagnosis via CTEP-AERS at <http://ctep.cancer.gov>
Report under ‘Secondary Malignancy – Other’
 3. Submit a copy of the pathology report to ECOG-ACRIN and NCI/CTEP confirming the diagnosis.
 4. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN and NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

5.4 Supportive Care

5.4.1 All supportive measures consistent with optimal patient care will be given throughout the study.

5.4.2 It is unknown whether bisphosphonates or other agents such as RANK ligand inhibitors at doses shown to prevent skeletal complication in hormone refractory disease is beneficial when a patient is just starting hormonal therapy. If a patient is to be treated with high dose bisphosphonates (not osteoporosis prevention dosing) then the investigator must declare this at the beginning to ensure patients treated in this manner are equally stratified to both arms. Once a patient is stratified, bisphosphonates at doses to prevent skeletal related events will be prohibited for patients who were not

Rev. 12/11

stratified by use of these agents. These patients can be treated with this class of drug at these doses once a skeletal related event occurs or once a patient develops hormone refractory disease. Osteoporosis prevention doses can be used at the investigator's discretion.

- 5.4.3 Medications to treat treatment-related side effects, such as nausea, hot flashes, diarrhea, are to be given at the investigator's discretion.

5.5 Duration of Therapy

Chemotherapy will be given for a maximum of six (6) cycles to patients on Arm A. Patients will come off study if they meet criteria for PSA or clinical progression.

Patients will receive protocol therapy unless:

- 5.5.1 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the E3805 Forms Packet.
- 5.5.2 Patient withdraws consent.
- 5.5.3 Unacceptable toxicity

At the time of hormone refractory disease investigators are encouraged to treat with docetaxel every three weeks ON BOTH ARMS so the effect of early versus delayed chemotherapy on overall survival can be performed. If the investigator deems that the patient is not a suitable candidate for docetaxel chemotherapy, the reason for this decision will be recorded. All therapy for hormone refractory disease will be recorded including anti-androgen withdrawal, second-line hormonal therapy and chemotherapy. If a patient has more than one therapy then all therapies will be recorded. Patients will be followed until development of HRPC and for overall survival.

5.6 Duration of Follow-up

For this protocol, all patients, including those who discontinue chemotherapy early, will be followed until development of hormone refractory disease and for survival for 10 years from the date of registration. All patients must also be followed through completion of all protocol therapy.

Rev. 7/08

6. Measurement of Effect

6.1 Solid Tumor Response Criteria (RECIST)

6.1.1 Malignant Disease Evaluation

To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Measurable disease is defined by the presence of at least one measurable lesion.

All measurements should be recorded in metric notation by use of a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified lesion at baseline and during follow-up. All baseline evaluations should be performed as detailed in Section [3](#).

The term evaluable in reference to measurability will not be used because it does not provide additional meaning or accuracy.

At baseline, tumor lesions will be characterized as either measurable or non-measurable.

6.1.1.1 Measurable

Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as > 20 mm (2.0 cm) with conventional techniques or as > 10 mm (1.0 cm) with **spiral** CT scan.

If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

6.1.1.2 Non-Measurable

All other lesions, including small lesions [longest diameter < 20 mm (2.0 cm) with conventional techniques or < 10 mm (1.0 cm) with **spiral** CT scan] and truly non-measurable lesions.

Lesions considered to be truly non-measurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Masses growing in a previously radiated field (e.g. prostatic fossa mass) are measurable if documented to have increased in size since XRT.

Rev. 7/08

6.1.2 Definitions of Response

6.1.2.1 Target Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs. Target lesions should be selected on the basis of their size (those with the longest diameters) and their suitability for accurate repeated measurements.

The sum of the longest diameters of all target lesions will be calculated at baseline and reported as the *baseline sum longest diameter*. The *sum longest diameter* will be used to characterize the objective tumor response. For lesions measurable in 2 or 3 dimensions, always report the longest diameter at the time of each assessment.

6.1.2.2 Complete Response (CR)

The disappearance of all target lesions. To be assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for response are first met.

6.1.2.3 Partial Response (PR)

At least a 30% decrease in the sum of the longest diameters of target lesions, taking as reference the *baseline sum longest diameter*. To be assigned a status of partial response, changes in tumor measurements must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for response are first met.

6.1.2.4 Progressive Disease (PD)

At least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the *smallest sum longest diameter* recorded since the baseline measurements, or the appearance of one or more new lesion(s).

6.1.2.5 Stable Disease (SD)

Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of at least 8 weeks.

6.1.3 Nontarget Lesions

All other lesions or sites of disease. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.1.3.1 Complete Response (CR)

The disappearance of all nontarget lesions and normalization of tumor marker levels, if applicable. To be assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for response are first met.

6.1.3.2 Incomplete Response/Stable Disease (SD)

The persistence of one or more nontarget lesion(s) and/or the maintenance of tumor marker levels above the normal limits. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of at least 8 weeks.

6.1.3.3 Progressive Disease (PD)

The appearance of one or more new lesion(s) and/or unequivocal progression of existing nontarget lesions.

6.1.4 Symptomatic Deterioration

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration.

Rev. 7/08

6.2 Evaluation of Patient's Best Overall Response

The best overall response is the best response recorded from registration until disease progression/recurrence, taking as reference for progressive disease the smallest measurements recorded since registration. The table below provides overall responses for all possible combinations of tumor responses in target and nontarget lesions, with or without new lesions.

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for response are first met.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of at least 8 weeks.

Overall Response for all Possible Combinations of Tumor Response

NOTE: For this protocol, measurable disease response is not being evaluated. However, time to radiographic progression is being evaluated and the following table will apply.

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

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

6.2.1 First Documentation of Response

The time between initiation of therapy and first documentation of PR or CR.

6.2.2 Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for response are first met.

6.2.3 Duration of Response

Duration of overall response – the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded since treatment started.

6.2.3.1 Duration of Overall Complete Response

The period measured from the time measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

6.2.3.2 Duration of Stable Disease

A measurement from registration until the criteria for disease progression is met, taking as reference the smallest measurements recorded since registration. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval or at least 8 weeks.

6.2.4 Methods of Measurement

Imaging based evaluation is preferred to evaluation by clinical examination. The same imaging modality must be used throughout the study to measure disease.

- 6.2.4.1 CT and MRI
- CT and magnetic resonance imaging (MRI) are the best currently available and most reproducible methods for measuring target lesions. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5 mm contiguous reconstruction algorithm. This specification applies to tumors of the chest, abdomen, and pelvis, while head and neck tumors, and those of the extremities require specific procedures.
- 6.2.4.2 Chest X-Ray
- Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by an aerated lung. However, CT is preferable.
- 6.2.4.3 Clinical Examination
- Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography, including a ruler to estimate size of the lesion, is recommended. Photographs should be retained at the institution.
- 6.2.4.4 Cytology and Histology
- Cytologic and histologic techniques can be used to differentiate between complete and partial response in rare cases (e.g., after treatment to differentiate residual benign lesions and residual malignant lesions in germ cell tumors). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met response or stable disease criteria.
- 6.2.4.5 Endoscopy and Laparoscopy
- Endoscopy and laparoscopy have not been fully or widely validated, so their use should be limited to validation studies in specialized institutions, and to confirming complete histopathologic response when biopsy specimens have been obtained.
- 6.2.4.6 Ultrasound
- Ultrasound may be used only as an alternative to clinical measurements for superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules, and for confirming complete disappearance of superficial lesions usually assessed by clinical examination.

6.3 Serological Response

6.3.1 Response According to PSA Levels

PSA levels will be assessed before hormone therapy, at time of randomization, then every 12 weeks thereafter. Patients PSA will be assigned a response according to the following criteria:

Complete Serological Response – PSA level less than 0.2 ng/mL measured for 2 consecutive measurements at least 4 weeks apart.

Serological Partial Response (PR) – decline of PSA value, referenced to the pre-androgen therapy level, by greater than or equal to 50% for 2 consecutive measurements at least 4 weeks apart.

PSA Stable Disease – Patients who do not meet the criteria for response (CR or PR) or serological progression for at least 3 months (90 days) will be categorized as having stable disease.

Serological Progression (PD) is observed when the PSA demonstrates an increase that is more than 50% of nadir, taking as reference the lowest recorded PSA level since starting androgen deprivation therapy (ADT). Two consecutive increases must be documented with each measurement obtained at least two weeks apart. On occasions, there may be an intermediate fluctuant value. In accordance with the recommendations of the Prostate Cancer Clinical Trials Working Group (51), this will **not** restart the evaluation period so long as the intermediate value was not below the previous nadir.

The date of first recorded increase (not defeated by a subsequent drop in PSA level to create a new nadir) will be deemed the *date of progression*.

If a patient achieves a PSA that is less than 4 ng/ml:

- The confirming increase must reach a value that is more than 4.0 ng/ml (the unconfirmed and additional intermediate increases may be a value that is less than 4.0 ng/ml, but greater than 50% of nadir since starting ADT).
- If the patient's nadir is less than 2 ng/ml, the first time the PSA reaches a value greater than 50% of nadir since starting ADT **and** is at least 2 ng/ml will be the date of first progression. However, this progression must be confirmed by a PSA value that is more than 4.0 ng/ml with no intervening declines below 2 ng/ml.
- Progression will be declared if patient has documented to have a testosterone less than 50 ng/dL. In cases where a testosterone level has not been obtained and patient has not had an orchiectomy (as detailed in the study calendar), PD will be deemed if patient had a documented rise in PSA on LHRH analogue therapy.

Rev. 7/08

Rev. 2/10

Rev. 12/11

6.3.2 Definitions of Serological Response

The following definitions of serological responses apply in this study:

First Documentation of Response – The period measured from the initiation of therapy until first documentation of partial or complete response.

Confirmation of Response – To be assigned a status of complete or partial response, changes in PSA level must be confirmed by repeat assessments performed *no less than 4 weeks* after the criteria for response are first met.

Duration of Response – The period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the first date that progressive disease is objectively documented, taking as reference the lowest PSA level recorded since androgen deprivation therapy started. Progression will be declared if patient has documented to have a testosterone less than 50 ng/dL. In cases where a testosterone level has not been obtained and patient has not had an orchiectomy (as detailed in the study calendar), PD will be deemed if patient had a documented rise in PSA on LHRH analogue therapy.

Duration of Complete Response – The period measured from the time that measurement criteria are met for complete response until the first date that progressive disease is objectively documented.

Time to Serological Progression – The period measured from the initiation of therapy until at least a $\geq 50\%$ increase in PSA level, taking as reference the lowest PSA level recorded since start of treatment. The date of the first recorded increase will be deemed the date of progression. If a patient achieves a PSA that is less than 4 ng/ml:

- The confirming increase must reach a value that is more than 4.0 ng/ml (the unconfirmed and additional intermediate increases may be a value that is less than 4.0 ng/ml, but greater than 50% of nadir since starting ADT).
- If the patient's nadir is less than 2 ng/ml, the first time the PSA reaches a value greater than 50% of nadir since starting ADT **and** is at least 2ng/mL will be the date of first progression. However, this progression must be confirmed by a PSA value that is more than 4.0 ng/ml with no intervening declines below 2 ng/ml.
- Progression will be declared if patient has documented to have a testosterone less than 50 ng/dL. In cases where a testosterone level has not been obtained and patient has not had an orchiectomy (as detailed in the study calendar), PD will be deemed if patient had a documented rise in PSA on LHRH analogue therapy.

Rev. 12/11

Rev. 2/10
Rev. 7/08

Rev. 7/08

Rev. 12/11

Rev. 7/08

6.4 Endpoint Definitions

6.4.1 Overall Survival

Survival will be measured as the period from randomization until death due to any cause.

6.4.2 Time to Hormone Refractory Disease:

The interval between randomization and the date of documented clinical or serological progression with testosterone less than 50 ng/dL.

Rev. 7/08

6.4.3 Time to Clinical Progression Free Survival:

The interval between randomization and the date of documented clinical progression. Clinical progression is defined as increasing symptomatic bone metastases, progression per RECIST criteria or clinical deterioration due to cancer per investigator's opinion.

Rev. 7/08

6.4.4 Time to Serological Progression Free Survival:

The interval between randomization and the date of documented PSA progression. Progression will be declared if patient has documented to have a testosterone less than 50 ng/dL. In cases where a testosterone level has not been obtained and patient has not had an orchiectomy (as detailed in the study calendar), PD will be deemed if patient had a documented rise in PSA on LHRH analogue therapy.

Rev. 12/11

6.5 Quality of Life (FACT-P)

As an additional secondary endpoint, Quality of Life, including benefit and adverse effects of the treatment and the disease, will be measured in all patients.

6.5.1 Overall Quality of Life

The Functional Assessment of Cancer Therapy-Prostate (FACT-P) is a self-report measure of both general and disease-specific quality of life (40). The FACT-P (version 4) contains 39 likert items distributed over 5 subscales: Physical (7 items), Social (7 items), Emotional (6 items), and Functional (7 items) well-being, and the additional concerns related to Prostate Cancer Scale (12 items). The FACT-P is scored by summing responses to the items in each subscale. The subscale scores are then combined to create a total QOL score. A trial outcome index (TOI) can also be calculated by summing the Physical and Functional Well-being Scales and the Prostate Cancer Scale. The FACT-P requires only a sixth-grade reading level and can be completed in 8 – 10 minutes (41).

The FACT-P scales have been widely used to evaluate quality of life in clinical trials for prostate cancer treatments. Internal consistency of the FACT-P (version 4) subscales ranges from .85 to .89. Concurrent, construct and discriminant validity has been documented (41).

Sensitivity to change in performance status and PSA score over two months has been demonstrated for the Physical Well-being, Functional Well-being, Prostate Cancer Scales, the Trial Outcome Index, and the total FACT-P (version 4) scale (41).

The FACT-P instrument has been validated in samples of patients with extensive disease prostate cancer (41), and used to assess

quality of life in studies of patients with extensive disease prostate cancer (42). However, treatment trials in this patient population have not always demonstrated a significant change in global measures of QOL, such as the FACT-P and the PROSQOLI (43,44). It has been hypothesized that for patients with extensive disease prostate cancer who are undergoing treatment, QOL is the product of both the alleviation of disease-related symptoms and the introduction of treatment-related symptoms (44). Thus, a thoughtful evaluation of the impact of the study treatment on QOL in this sample will require that in addition to overall QOL, disease-related symptomatology and treatment-associated symptomatology symptoms must be assessed, as well.

6.5.2 Treatment-associated and Disease-associated Symptoms

The FACT-Taxane instrument is a sub-scale developed to supplement QOL assessment by the FACT scales. It is a 16-item scale that assesses patients' experience of the symptoms most commonly associated with taxane treatment, and has been validated for this purpose (40). The FACT-Taxane subscale has been demonstrated to have excellent internal consistency reliability, validity and responsiveness to change over time (40). Significant decreases in the FACT-Taxane scale have been demonstrated to coincide with the emergence of neurotoxicity in patients undergoing taxane treatment and the relationship of the FACT-taxane score to duration of taxane treatment is linear (40).

Approximately 90% of patients undergoing taxane treatment experience anemia (45). A clinical symptom associated with anemia, fatigue is also a prevalent correlate of extensive disease prostate cancer (44,46). Thus, fatigue, a negative correlate of QOL in cancer patients in general, as a correlate of both extensive disease prostate cancer and the treatment in Arm A, can be expected to play a particularly important role in the evaluation of QOL in this study.

Fatigue will be evaluated using the 13-item Fatigue Subscale of the FACIT-F, which was developed to assess the physical experience of fatigue in cancer patients (47,48). Summed with the four core subscales of the FACT-P (Physical, Social, Emotional and Functional) it creates the Functional Assessment of Cancer Therapy-Fatigue (FACIT-F) score, a measure of both the physical experience and the functional consequences of fatigue (47,48). The Fatigue Subscale and the FACIT-F exhibit strong convergent and discriminant validity, internal consistency, test-retest reliability, and sensitivity to group differences in performance status (47,48).

Pain is the dominant disease-associated symptom experienced by men with metastatic prostate cancer. Therefore, reduction in pain has been the most significant palliative endpoint in treatment trails in this population. Pain will be assessed using the Brief Pain Inventory (BPI) Short Form (49). The BPI is a rapidly and easily completed self-report instrument, designed to measure pain intensity, interference with daily functioning, and relief. Reliability and validity of the BPI are well-established (49, 50).

7. Study Parameters

7.1 Therapeutic Parameters

Rev. 7/08

1. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done within 6 weeks prior to randomization. (See Section [3.1.2](#) for guidance if hormonal therapy commenced prior to obtaining all scans).

2. Prestudy CBC (with differential and platelet count) should be done ≤ **4 weeks** before randomization.

Rev. 7/08

3. All required prestudy chemistries, as outlined in Section [3.1.4](#), should be done ≤ **4 weeks** before randomization – unless specifically required on Day 1 as per protocol.

Rev. 2/07

| Visit/ Assessment | Baseline | Day 1, Cycle 1 | Day 1, Cycles 2-6 | Follow-up; Every 3 months ⁶ | Hormone Refractory |
|---|--------------------------------------|------------------|-------------------|--|--------------------|
| Arm A | | | | | |
| Physical Examination, Vital Signs | X | X ^{2,5} | X ⁵ | X | |
| CBC with diff, Platelets ¹ | X | X ² | X ¹ | | |
| Creatinine clearance, PTT, PT, INR | X | X ² | | | |
| Total Bilirubin, ALT | X | X ² | X ¹ | | |
| Arm B | | | | | |
| Physical Examination, Vital Signs | X | X ² | | X | |
| CBC with diff, platelets ¹ | X | | | | |
| Creatinine clearance, PTT, PT, INR | X | | | | |
| Both Arms A and B | | | | | |
| Medical History, ECOG PS | X | | | | |
| CT Abdomen/Pelvis | X | | | | X |
| Chest X-ray/CT chest ³ | X | | | | X |
| Bone Scan | X | | | | X |
| [Deleted Addendum #3] | | | | | |
| FACT-P, FACT-Taxane, FACIT-F, and the BPI | X | | X ⁷ | X ⁸ | |
| PSA | X | | X ⁹ | X | X |
| Testosterone | | | | | X ⁴ |
| Biological Sample Submissions | Refer to Section 7.2 | | | | |

Rev. 7/08

1 CBCs (with differential and platelet count which includes WBC, ANC, Platelets, Hgb, and Hct) and ALT and total bilirubin which are required for protocol therapy on days 1 of cycles 2-6, must be done day prior to or day of treatment with docetaxel. If holidays or weather prevent treatment on day 1 as planned, day 1 will be the next feasible day of treatment and should be no more than a 7 day delay.

2 Does not need to be repeated if within 7 days of screening PE.

Rev. 7/08

3 All patients must at least have a CXR prior to randomization to assess status of disease. CT chest at investigator's discretion. CXR within 6 weeks of starting hormonal therapy is required. (See Section [3.1.2](#) for guidance if hormonal therapy commenced prior to obtaining all scans).

4 To document castrate level at progression if patient has not had a bilateral orchiectomy.

5 Physical examinations can be done up to 72 hours prior to dosing of docetaxel.

Rev. 2/07, 7/08

6 Follow up every 3 months will continue beyond the time of HRCPC for overall survival and will require

physical examination and PSA measurements and recording of all subsequent therapy.

Follow-up Schedule:

- Rev. 7/08
- Every 3 months if patient is < 2 years from study entry
 - Every 6 months if patient is 2-5 years from study entry
 - Every 12 months if patient is 5-10 years from study entry
 - If patient is > 10 years from study entry, no forms are required
- Rev. 2/07 7 For both Arms A and B, submit at 3 months (12 weeks).
- Rev. 2/07 8 For both Arms A and B, submit at the end of months 6, 9, and 12.
- Rev. 7/08 9 For Arm A only (i.e., only patients getting docetaxel).

Rev. 2/07, 12/11
1/15, 9/16

7.2 Biological Sample Submissions

Samples for the correlative studies should be submitted as outlined in Sections [10](#) and [11](#). Collection and submission of samples is to be limited to those patients who have given written consent to participate in the correlative studies or banking or both.

NOTE: ECOG-ACRIN requires that all biological samples submitted from patients participating in this trial be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See Section [10.4](#).

NOTE: As of March 31, 2016 collection of blood samples is closed.

| Samples | | Baseline | Week 24 ² | Progression | Submit to: |
|---------------------------|---------------------------------|--|----------------------|-------------|--|
| Prostate Cancer Pathology | | X | | | ECOG-ACRIN CBPF (Section 10.2) |
| Peripheral Blood | 6 mL EDTA lavender top tube | Blood Collection Closed March 31, 2016 | | | HCRN ³ (Section 10.3) |
| Plasma | 6 mL EDTA lavender top tube x 2 | | | | |
| Serum | 10 mL red top tube | | | | |

1. Baseline draws are to be collected AFTER randomization, prior to start of treatment. No samples are to be submitted prior to randomization.
2. If the indicated draws were missed, draw at the next scheduled clinical draw and note in STS, upon submission, the cycle, week number, and day that samples were taken.
3. Kits are available to order and will include all supplies needed for the collection and the shipping of the samples. It is important to only use the collection kits and shippers that the Hoosier Cancer Research Network provides. To order kits, fax Kit Order Form ([Appendix VI](#)) to Mayan Howard and Michael Nunley at (317) 921-2053.

Rev. 1/15

8. Drug Formulation and Procurement

8.1 Docetaxel

Please refer to the FDA approved package insert for additional information.

8.1.1 Other Names

Taxotere, RP 56976, NSC #628503.

8.1.2 Classification

Antimicrotubule agent.

8.1.3 Mode of Action

Docetaxel, a semisynthetic analog of taxol, promotes the assembly of tubulin and inhibits microtubule depolymerization. Bundles of microtubules accumulate and interfere with cell division.

8.1.4 Storage and Stability

Store intact vials between 2° and 25°C (36° and 77°F). Retain in the original package to protect from bright light. The final dilution (in either 0.9% sodium chloride or 5% Dextrose solution) is stable for 4 hours if stored between 2° and 25°C (36° and 77°F).

8.1.5 Dose Specifics

75 mg/m² of docetaxel will be given on day 1 every 21 days for a maximum of six (6) cycles.

8.1.6 Preparation

Just prior to use, allow the docetaxel vial to reach room temperature for 5 minutes. Add the entire contents of the ethanol diluent vial and mix by gently rotating the vial for 45 seconds. Allow to stand for 5 minutes at room temperature, and check that the solution is homogeneous and clear (persistent foam is normal). The resulting solution contains 10 mg/mL of docetaxel. Please note that the solution contains 15% overfill. Dosing amounts should be based in the concentration per extractable volume, not the total volume of the vial. The desired dose is diluted in D5W or NS. The volume of the infusion should be adjusted in order to have a final docetaxel concentration of between 0.3 mg/mL and 0.74 mg/mL. Non-PVC-containing intravenous infusion bags and administration sets should be used to avoid patient exposure to the plasticizer DEHP.

8.1.7 Administration

Docetaxel will be administered to patients as an IV infusion over approximately one hour.

8.1.8 Incompatibilities

Intravenous bags and administration sets containing DEHP (di-[2-ethylexy] phthalate). No further information available.

Rev. 6/14

8.1.9 Availability

Docetaxel is a commercially marketed product which has been approved by the FDA for: the treatment of locally advanced or metastatic breast cancer that returns after any prior chemotherapy; locally advanced or metastatic non-small cell lung cancer that recurs after prior platinum-based chemotherapy; and in combination with prednisone for the treatment of advanced metastatic prostate cancer. However its use in patients eligible for this protocol with prostate cancer is not currently approved by the FDA. When used as directed by this protocol, docetaxel is classified as an "unapproved use of an approved agent" and, by definition, considered as an investigational agent. However, while it is not an indication currently approved by the FDA, the use of docetaxel in this protocol is exempt from the requirements of an IND as described under Title 21 CFR 312.2(b).

NOTE: During the course of this study, if the FDA approves docetaxel for use in patients with prostate cancer, then the patient may have to pay for the amount of drug needed to complete the study.

Docetaxel (Taxotere[®]) is available and distributed free of charge from Sanofi-Aventis Pharmaceuticals. The vials of docetaxel will be packaged as 80 mg/2 mL vials. The initial shipment will be 6 vials, enough for 3 cycles. Vials of diluent will also be included.

After patient randomization, a supply of docetaxel may be obtained. Investigators must fax a signed and completed "E3805 Clinical Supplies Shipping Form" ([Appendix VII](#)) to the ECOG-ACRIN Operations Office – Boston, ATTN: Drug Team at 617-632-2063. Do not send drug requests directly to Sanofi-Aventis Pharmaceuticals. Allow 4-5 business days for receipt of the drug. See below for re-ordering instructions.

During the Study

There will be no weekend or holiday delivery of drugs. All deliveries will be made by express carrier.

Receipt of drug shipment: Complete the "Receipt From" section of the shipping form and fax to Debra Dawson at 908-243-7745.

Reorders: Each institution is responsible for reordering study drug. Complete and fax the E3805 Clinical Supplies Shipping Form ([Appendix VII](#)) to the ECOG-ACRIN Operations Office – Boston at 617-632-2063. Please allow 4-5 business days for processing reorders.

Drug Inventory Records: The Investigator or a responsible party, designated by the investigator, must maintain careful record of the inventory and dispensation of all drugs received. Please use the NCI Drug Accountability Record Form or equivalent. (See the NCI Investigators Handbook for Procedures for Drug Accountability and Storage.) The unused docetaxel must be accounted for.

At the Completion of the Study:

At the completion of the study, all used and unused drugs may be destroyed at the site, in accordance with the applicable regulations, guidelines and institution's procedures. Please maintain appropriate records of the disposal, including dates, quantities and method of destruction.

8.1.10 Side Effects

1. Cardiac: arrhythmias, pericardial effusions.
2. Hematologic: dose-related neutropenia, leukopenia, thrombocytopenia, anemia, hypoglycemia, hypernatemia.
3. Gastrointestinal: nausea and vomiting, diarrhea, oral mucositis, pancreatitis, esophagitis.
4. Neurologic: reversible dyesthesias or paresthesias, peripheral neuropathy, mild or moderate lethargy or somnolence, headache, seizures.
5. Hypersensitivity: hypersensitivity (local or general skin rash, flushing, pruritus, drug-fever, chills and rigors, low back pain), severe anaphylactoid reactions (flushing with hypo- or hypertension, with or without dyspnea).
6. Dermatologic: alopecia, desquamation following localized pruriginous maculopapular eruption, skin erythema with edema, extravasation reaction (erythema, swelling, tenderness, pustules), reversible peripheral phlebitis, nail changes.
7. Hepatic: increased transaminase, alkaline phosphatase, bilirubin; hepatic failure; hepatic drug reaction.
8. Pulmonary: dyspnea with restrictive pulmonary syndrome, pleural effusions.
9. Other: asthenia, dysgeusia, anorexia, conjunctivitis, arthralgia, muscle aches, myopathy, peripheral edema, fluid retention syndrome, ascites.

8.1.11 Nursing Implications

1. Monitor CBC and platelet count prior to drug administration.
2. Symptom management of expected nausea, vomiting, and mucositis.
3. Advise patients of possible hair loss.
4. Monitor for signs and symptoms of hypersensitivity reactions. Insure that recommended premedications are given.
5. Monitor liver function tests.
6. Evaluate site regularly for signs of infiltration.
7. Monitor for symptoms of peripheral neuropathy.
8. Monitor for signs of fluid retention and cutaneous reactions.

8.1.12 References

Investigator's Brochure: Docetaxel. Rhone-Poulenc Rorer, June 14, 1995.

Pazdur R, *et al.* Phase I trial of Taxotere; Five-day schedule. *J Natl Cancer Inst* 84:1781-8, 1992.

Pazdur R, *et al.* Phase I trial of Taxotere (RP56976). *Proc Am Soc Clin Oncol* 11:111, 1992.

Burriss H, *et al.* A phase I clinical trial of Taxotere as a 6-hour infusion repeated every 21 days in patients with refractory solid tumors. *Proc Am Soc Clin Oncol* 11:137, 1992.

Bissett D, *et al.* Phase I study of Taxotere (RP56976) given as a 24-hour infusion. *Proc Am Assoc Cancer Res* 33:526, 1992.

Bruno R, *et al.* Clinical pharmacology of Taxotere (RP56976) given as a 1-2 hour infusion every 2-3 weeks. *Proc Am Assoc Cancer Res* 33:261, 1992.

DeValeriola D, *et al.* Phase I pharmacokinetic study of Taxotere (RP56976) administered as a weekly infusion. *Proc Am Assoc Cancer Res* 33:1563, 1992.

Rev. 12/11

8.2 LHRH analogue (such as leuprolide, goserelin, lcape degarelix)

Please refer to the FDA approved package insert for additional information.

8.2.1 Description:

Rev. 12/11

LHRH analogues are long-acting analogs of the native LHRH peptide and are effective at reducing serum testosterone. Analog approved by the FDA can be used in this study.

8.2.2 Supply:

Commercial available.

8.2.3 Administration:

LHRH analogs are administered with a variety of techniques such as subcutaneously, intramuscularly, or insertion. The manufacturer's instructions should be followed.

8.2.4 Toxicity:

The most common side effect is vasomotor hot flashes; edema, gynecomastia, bone pain, thrombosis, and gastrointestinal disturbances. Other side effects include impotence and loss of libido, weight gain, depression, dizziness, anemia, skin redness, pain at the injection site, unusual taste in the mouth, increased thirst and urination, and rarely allergic generalized rash and difficulty breathing.

8.3 Antiandrogens (flutamide and bicalutamide)

Please refer to the FDA approved package insert for additional information.

8.3.1 Availability:

Commercial available.

8.3.2 Administration:

The drugs are administered orally as prescribed.

8.3.3 Toxicity (flutamide):

Diarrhea and anemia. A high percentage of patients treated with flutamide alone developed gynecomastia within 2 to 8 months. There have been post marketing reports of hospitalization, and rarely, death due to liver failure in patients taking flutamide. Other side effects include elevated transaminase levels, jaundice, hepatic encephalopathy, and death related to acute hepatic failure, which is reversible after prompt discontinuation in some patients; impotence and loss of libido, fatigue, and rarely photosensitivity.

8.3.4 Toxicities (bicalutamide):

Breast tenderness, breast swelling, and hot flashes. When bicalutamide 50 mg was given in combination with an LHRH analog, the LHRH analog adverse event profile predominated with a high incidence of hot flashes (53%), and relatively low incidences of gynecomastia (4.7%) and breast pain (3.2%). Other side effects include impotence and loss of libido, fatigue, and rarely photosensitivity.

9. Statistical Considerations

Rev. 12/11

9.1 Introduction

This is the second revision of the statistical considerations section. The first changes reflect design changes incorporated in addendum 3. Addendum 3 expanded study eligibility to all patients with both low and high volume metastatic disease; eligibility was no longer restricted to patients with high volume disease. High volume disease is defined as visceral metastases and/or bone metastases (at least 4 or more bone lesions, and one of which must be outside of the vertebral column AND pelvis). The duration between beginning of prior hormonal therapy and registration was also changed from 90 days to 120 days. Furthermore, an additional stratification factor was added in this addendum, extent of disease: high vs. low volume disease.

Rev. 6/14

The second revision is to increase the number of patients to be accrued from 600 patients to 780 patients. This is based on data from S9346 demonstrating that the overall survival of men with prostate cancer starting androgen deprivation therapy (ADT) in the modern era is longer than the historical data which was used to develop the assumptions of addendum 3. In addition, the estimated proportion of patients with high volume disease is also changed based on the preliminary data released from the ECOG-ACRIN Data Monitoring Committee (DMC) meeting in September, 2011. As such, the projections which are guiding the statistical design need to be updated and require a trial of 780 patients.

9.2 Endpoints

The primary clinical endpoint is the difference across treatments in overall survival. Patients will be stratified based on age, ECOG PS, use of combined androgen blockade and FDA approved drugs for delaying skeletal related events, time of prior adjuvant hormonal therapy, and extent of disease; no subgroup analyses are planned. Primary endpoint will be studied for all intent-to-treat patients.

Secondary endpoints include PSA response, change of PSA over time, time to hormone refractory disease, time to clinical progression and time to PSA progression. All patients who receive treatment, regardless of eligibility, will be evaluated for toxicity.

9.3 Sample Size and Accrual

Based on prior studies and the preliminary data from SWOG study S9346, there will be approximately 50% of patients with high volume disease and 50% of patients with low volume disease in this population. Median survivals in arm B were expected to be 24 months and 48 months for patients with high and low volume disease, respectively. Under these assumptions above, the study required 600 patients to be accrued and randomized equally to each of the two arms (300 patients per arm). With the projected accrual rate of 8 patients per month, the accrual goal was to be reached in 75 months with a follow up period of 2.5 years.

Data from S9346 in the modern era indicates that median overall survival of men treated with ADT and having low volume disease is approximately 67 months. The median overall survival for men with high volume disease is 33 months. This

is probably due to active agents for castrate resistant prostate cancer and stage migration. The study is designed to demonstrate a 25% reduction in the survival hazard rate, which corresponds to an improvement in median overall survival from 33 months to 44 months in patients with high volume disease and from 67 months to 89.3 months in patients with low volume disease. After the activation of addendum 3, E3805 was enrolling approximately 12 patients per month and exceeds the anticipated accrual rate of 8 patients per month detailed in addendum 3. In addition, based on the preliminary data released from the DMC meeting in September, 2011, about 70% of patients have high volume disease on this study. With the assumptions above, the study will need 780 patients to maintain adequate power, and the accrual will be completed in 5.5 years with additional 1.5 years for follow-up.

9.4 Primary Objective

The study will have 80% power to detect a 33.3% improvement in median overall survival across treatments, using a log-rank test stratified on age, ECOG PS, use of combined androgen blockade and FDA approved drugs for delaying skeletal related events, time of prior adjuvant hormonal therapy, and extent of disease with a one-sided 0.025 significance level. The primary comparison will be an intent-to-treat analysis including all randomized patients.

Interim analyses will be performed for all semi-annual ECOG-ACRIN DMC meetings beginning when approximately 25% of the planned full information has occurred, about 35.5 months, continuing every 6 months until either criterion for early stopping are met or full information is reached. Twenty-five percent of the full information under the alternative hypothesis is equal to 100 failures. Full information will be achieved when 399 patients have died. The final analysis is scheduled for this time point. This study will be monitored for early stopping in favor of the null hypothesis using repeated confidence interval methodology similar to that described by Jennison and Turnbull, 1990 (Statistical Science 5:299-317). At each interim analysis the nominal $(1-2 \times \alpha)$ confidence interval on the overall survival hazard ratio comparing arm B to arm A will be computed, where α is the nominal one-sided significance level of the use function boundary at the information fraction for the particular analysis time. If the upper bound of the repeated confidence interval is smaller than 1.33, then the data monitoring committee may consider closing an arm of the trial or stopping the study early for overall lack of treatment differences. Under the accrual and failure rate assumptions above, the following table gives the expected interim analysis times, information times, and the corresponding truncated O'Brien Fleming boundaries (K. Lan and D. DeMets, 1983, Biometrika 70(3):659-663). Information from interim analyses will be reviewed by the DMC, who may decide to stop the study early if efficacy or futility has been demonstrated. Because of delays in initiation of accrual and delays in data submission and processing, it is likely that the actual analysis times will be 6-12 months later.

| Repeated Analyses | Real Time (Months) | Information Time | Number of Failures | | P-value | Upper Boundary | Number of Patients |
|-------------------|--------------------|------------------|--------------------|----------|---------|----------------|--------------------|
| | | | Under Ho | Under H1 | | | |
| 1 | 35.5 | 0.25 | 108.85 | 99.87 | 0.0005 | 3.29 | 426 |
| 2 | 41.5 | 0.33 | 143.88 | 132.01 | 0.0005 | 3.29 | 498 |
| 3 | 47.5 | 0.42 | 182.44 | 167.39 | 0.0005 | 3.29 | 570 |
| 4 | 53.5 | 0.52 | 224.17 | 205.68 | 0.0010 | 3.08 | 642 |
| 5 | 59.5 | 0.62 | 268.74 | 246.57 | 0.0035 | 2.69 | 714 |
| 6 | 65.5 | 0.73 | 315.82 | 289.77 | 0.0070 | 2.46 | 780 |
| 7 | 71.5 | 0.83 | 360.92 | 331.15 | 0.0109 | 2.29 | 780 |
| 8 | 77.5 | 0.92 | 401.27 | 368.17 | 0.0148 | 2.18 | 780 |
| 9 | 83 | 1.00 | 434.54 | 398.69 | 0.0180 | 2.10 | 780 |

9.5 Randomization and Stratification

Randomization will be performed with the following stratifications: 1) age: ≥ 70 vs. < 70 ; 2) ECOG PS: 0-1 vs. 2; 3) intended use of combined androgen blockade greater than 30 days from start of therapy; 4) prior adjuvant hormonal therapy > 12 months vs. ≤ 12 months; 5) use of FDA approved drugs for delaying skeletal related events; and 6) extent of disease: high volume vs. low volume disease.

The method of permuted blocks will be used for subject randomization. No per-site treatment-allocation balance will be implemented.

9.6 Quality of Life Analysis

The primary quality of life objective is to describe quality of life over time within each arm. Quality of life will be evaluated at baseline (within 1 week prior to therapy), week 12, week 24, week 36 and week 48. The primary comparison of interest will be the comparison between baseline (pre-treatment) and week 12 for scores on the FACT-P instrument. Treatment-associated and disease-associated changes in QOL will also be compared between baseline and week 12 for scores on the FACIT-F Fatigue Subscale, FACT-Taxane Subscale and the Brief Pain inventory. A comparative analysis will also be performed between arms A and B at each time point.

There are two sources of missing assessments in this study. The first source of missing assessments is among patients who are alive but do not complete the assessment, for reasons such as missed appointments, staff forgetting to administer the instrument, or patient refusal. We assume that this missingness is random, and will analyze the remaining questionnaires under this assumption. We expect only about 2% of the assessments to be missing at baseline, 10% by week 12, and about 30% to be missing by 24 weeks. The other type of

missingness is due to patients who will die during the study. If the median survival is 3-5 years and we assume that deaths follow an exponential distribution, we would expect about 3%-6% of the patients to have died by week 12. Because quality of life is likely to be related to survival, this censoring may be non-ignorable. For this reason, the comparison of week 12 to baseline will be considered the primary analysis.

We expect 85% to be alive and have completed baseline and week 12 assessments. A paired t-test will be used to test the null hypothesis that the change in quality of life score is not equal to 0 for each arm. Assuming 330 patients on each arm with measures on both days and a two-sided test with $\alpha=0.05$, we have 90% power to detect a difference of 0.18 standard deviation. This translates into a change of about 2.6 points assuming the standard deviation of the difference is 14.5 points, which was the standard deviation of the difference in QOL scores between baseline and week 8 from patients in E1898. Differences in quality of life between treatment arms will also be of interest. A t-test will be used to test for pairwise differences between treatment arms at week 12. Assuming a two-sided test with $\alpha=0.05$, the study will have about 90% power to detect a difference of 0.25 standard deviation between two treatment arms. This translates into a change of about 3.6 points assuming the common standard deviation is 14.5 points. Methods developed by Schluchter (1992) will be used to jointly model quality of life and survival data adjusting for non-ignorable missing data due to death or patient withdrawal. Similar analyses will be performed on the FACIT-F Fatigue Subscale scores, FACT-Taxane Subscale score and the Brief Pain inventory scores.

9.7 Gender and Ethnicity

Based on the preliminary data from **S9346**, the anticipated accrual in subgroups defined by gender and race is:

| Ethnic Category | Gender | | |
|---|---------|-------|-------|
| | Females | Males | Total |
| Hispanic or Latino | 0 | 34 | 34 |
| Not Hispanic or Latino | 0 | 746 | 746 |
| Ethnic Category: Total of all subjects | 0 | 780 | 780 |
| Racial Category | | | |
| American Indian or Alaskan Native | 0 | 3 | 3 |
| Asian | 0 | 12 | 12 |
| Black or African American | 0 | 87 | 87 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| White | 0 | 678 | 678 |
| Racial Category: Total of all subjects | 0 | 780 | 780 |

Rev. 12/11
Rev. 1/15,
4/15, 9/16

10. Sample Submissions

Blood and tissue samples are to be submitted from consenting patients for the laboratory research projects defined in Section [11](#) and for possible use in future research projects.

ECOG-ACRIN requires that all samples submitted on this trial be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). An STS shipping manifest from must be generated and shipped with the sample submissions. See Section [10.4](#).

10.1 Submission Summary

No samples are to be submitted prior to patient randomization.

Tissue sample submissions are outlined in Section [10.2](#) are to be submitted from patients who answer “Yes” to “*I agree to participate in the scientific laboratory research studies that are being done as part of this clinical trial*” or “*My specimens may be kept for use in research to learn about, prevent, treat, or cure cancer.*”

Blood samples submissions are outlined in Section [10.3](#) and are to be submitted from patients who answer “Yes” to “*I agree to participate in the scientific laboratory research studies that are being done as part of this clinical trial.*” Instructions for ordering the collection/shipping kits are outlined in Section [10.3](#). Note that international sites outside the United States and Canada are not required to submit the blood samples because of the costs and problems associated with international shipping.

NOTE: As of March 31, 2016 collection of blood samples is closed.

| Samples | | Baseline | Week 24 ¹ | Progression | Submit to: |
|---------------------------|---------------------------------|---|----------------------|-------------|---|
| Prostate Cancer Pathology | | X | | | ECOG-ACRIN CBPF (Section 10.2) |
| Peripheral Blood | 6 mL EDTA lavender top tube | Blood Collection Closed March 31, 2016 | | | HCRN (Section 10.3) |
| Plasma | 6 mL EDTA lavender top tube x 2 | | | | |
| Serum | 10 mL red top tube | | | | |

1. If the indicated draws were missed, draw at the next scheduled clinical draw and note in STS, upon submission, the cycle, week number, and day that samples were taken.

10.2 Pathology Submissions

Tumor tissue from the prostatectomy specimen is preferred, but if not available please send biopsy specimen from either prostate or metastatic site. Submit from patients who have given written consent for the use of their samples for the laboratory research studies or for possible use in future research.

When a patient is registered to receive protocol therapy, the submitting pathologist and clinical research associate should refer to [Appendix II](#) (Pathology Submission Guidelines), for submission requirements.

10.2.1 The materials to be submitted are:

Forms:

- A copy of the surgical pathology report, if available.
- STS generated shipping manifest
- If STS is down, please complete an ECOG-ACRIN Generic Specimen Submission Form (#2981). Please identify the clinical status of the submitted material (i.e., pretreatment as opposed to remission and relapse).

Biological Material Submission

Indicate in STS whether the tumor tissue materials are from the prostatectomy (preferred) or prostate biopsy or metastatic site.

- One representative tumor block.

NOTE: If a tumor block is unavailable, one tissue core punch, 10 unstained positively charged slides (3-4 microns), and one (1) H & E slide may be substituted.

10.2.2 Shipping Procedures

Submit at ambient temperature within one month following randomization to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

10.2.3 Central Biorepository and Pathology Facility: Sample processing and Routing

As outlined in Section [11](#), the appropriate materials for the protocol-defined correlative studies will be distributed to investigators for analysis. Residuals will be stored for future research.

10.3 Blood Specimen Submissions

NOTE: As of March 31, 2016 collection of blood samples is closed.

Sample draws are requested as follows:

- Baseline, after randomization prior to treatment: serum, plasma, peripheral blood*
- Week 24*: serum, EDTA plasma
- Note: if this time point is missed, please draw at the next scheduled clinical draw.
- Progression: serum, plasma

*If any draws are delayed, in the comment field of STS indicate the actual cycle, week number, and day that samples were collected.

10.3.1 Kit Requests

To order kits, complete Kit Order Form ([Appendix VI](#)) and fax to Mayan Howard and Michael Nunley at (317) 921-2053.

A minimum of five (5) working days notice of kit needs is required. Kits will NOT be shipped by overnight courier unless expressly stated on the form that the kit is needed within 24 hours due to patient enrollment. The first kit request may be done upon institutional IRB approval.

Collection kits will be provided and will contain everything needed for the sample collections and shipping. **It is important to ONLY use the collection kits and shippers provided by the Hoosier Cancer Research Network.**

10.3.2 Sample Preparation

Complete the pre-printed cryovial labels for the appropriate timepoints (baseline, week 24 or progression) using only a Sharpie marker. Fill in the patient initials, date of collection, and ECOG-ACRIN patient ID number then place on relevant cryovial (this should be done before the cryovials are frozen).

10.3.2.1 Red Top Tube

Collect at baseline, week 24, and progression.

SERUM SAMPLES MUST BE FROZEN WITHIN ONE HOUR OF BLOOD DRAW.

- Draw approximately 10 ml of blood into the red top vacutainer tube.
- Allow to coagulate for 30 minutes,
- Centrifuge at 3500 rpm for 30 minutes.
- Without delay, divide the serum equally into three (3) labeled cryovials in approximately 1.5 ml aliquots.
- Freeze immediately at -70°C until time of shipment. If a -70°C freezer is not available serum samples may be stored at -20°C until shipped. Samples **MUST** be shipped via Fed-Ex priority overnight as soon as possible. **DO NOT ALLOW THE SAMPLES TO THAW.**

10.3.2.2 EDTA Lavender Top Tubes

Whole Blood Processing

Collect at baseline. If baseline is missed, collect at next scheduled draw.

- Draw 6 mL of whole blood into one EDTA lavender top tube.
- Invert gently then divide sample equally into two (2) labeled cryovials.

- Freeze immediately at -70°C until time of shipment. If a -70°C freezer is not available samples may be stored at -20°C until shipped. Samples MUST be shipped via Fed-Ex priority overnight as soon as possible. DO NOT ALLOW THE SAMPLES TO THAW.

Plasma Processing

Collect at baseline, week 24, and progression.

SAMPLE PROCESSING MUST BE STARTED WITHIN 30 MINUTES OF BLOOD DRAW.

- Draw approximately 6 mL of blood into each of the two EDTA lavender top vacutainer tubes.
- Invert gently.
- Centrifuge them at 3500 rpm for 30 minutes.
- Without delay, divide plasma equally into six (6) labeled cryovials in ~ 1 ml aliquots, and then freeze the samples immediately at -70°C. If a -70°C freezer is not available, plasma samples may be stored at -20°C until shipped. Samples MUST be shipped as soon as possible and sent by overnight courier, DO NOT ALLOW SAMPLES TO THAW.

Rev. 4/15

10.3.3 Shipping Guidelines

If multiple patients' samples are shipped together, bag each patients' samples separately using provided baggies. Make sure that cryovials are double-bagged for shipment) The STS-generated shipping manifest must accompany the samples. If STS is unavailable, see Section [10.4](#).

Using only the ThermoSafe shippers provided by the Hoosier Cancer Research Network, completely fill the shipper with dry ice covering the samples.

Ship Monday through Thursday only (to arrive Tuesday through Friday). Shipments that arrive on Saturdays and holidays will NOT be accepted. The HCRN laboratory must be contacted PRIOR to shipping, email notification to: Mayan Howard – mhoward@hoosiercancer.org and Michael Nunley – mnunley@hoosiercancer.org or call at (317) 921-2050. Please include the Fed-Ex tracking number in the email.

Ship samples to:

Hoosier Cancer Research Network
Attn: Mayan Howard/Michael Nunley
500 North Meridian Street
Suite 100
Indianapolis, IN 46204

NOTE: If your facility does not have dry-ice, contact Mayan Howard or Michael Nunley to review potential sources.

10.4 ECOG-ACRIN Sample Tracking System

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking <https://webapps.ecog.org/Tst>.

Important: Any case reimbursements associated with specimen submissions may not be captured if specimens are not logged into STS. Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: <http://www.ecog.org/general/stsinfo.html>. Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest should be generated and shipped with all sample submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu.

Study Specific Notes

If the STS is unavailable,

- ECOG-ACRIN CBPF
FAX the completed ECOG-ACRIN Generic Specimen Submission Form (#2981) to the ECOG-ACRIN CBPF at 1-844-744-2420. Include the Fed-Ex tracking number in the comment section of the form.
- Hoosier Cancer Research Network (HCRN):
The day the samples are shipped, substitute the STS-generated shipping manifest with a completed E3805 Specimen Submission Form (#2741) AND email Mayan Howard – mhoward@hoosiercancer.org and Michael Nunley – mnunley@hoosiercancer.org and or call (317) 921-2050. Include the Fed-Ex tracking number in the comment section of the form.

Retroactively enter all specimen collection and shipping information when STS is available.

10.5 Banking

Residual material from the specimens submitted will be retained at the ECOG-ACRIN Central Biorepository for possible use in future ECOG-ACRIN approved studies. Any residual blocks will be available for purposes of individual patient management on specific written request. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

10.6 Sample Inventory Submission Guidelines

Inventories of all samples submitted will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized for the will be submitted by the laboratory to the ECOG-ACRIN Operations Office – Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office – Boston.

10.7 Lab Data Transfer Guidelines

The data collected and generated on the laboratory research studies will be submitted electronically using a secured data transfer to the ECOG-ACRIN Operations Office – Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the investigator. The quarterly cut-off dates are March 31, June 30, September 30, and December 31. Quarterly data reports are due at the ECOG-ACRIN Operations Office – Boston 1 week after these cut-off dates.

Rev. 12/11,
9/16

11. Correlative Studies

Blood and tissue samples are to be submitted as outlined in Section [10](#) for use in the laboratory research studies described below. As technologies are developed and refined, the samples from E3805 will be used for additional research projects to explore various additional biological parameters, including molecular and genetic, and their relevance to prostate cancer. Any additional projects will only be conducted after receipt of the appropriate reviews and approvals.

11.1 Proteomic Study

This correlative study is administratively withdrawn effective March 1, 2016.

Two-dimensional polyacrylamide gel electrophoresis (2D PAGE) has been the principal tool for the separation and simultaneous analysis of multiple proteins (20). This methodology, which is able to resolve numerous proteins in one experiment, provides the highest resolution in protein separation. Although the resolving power of 2D PAGE remains unchallenged, the high sensitivity, speed and reproducibility of mass spectrometry-based approaches have boosted their application in all aspects of protein analysis, including profiling, discovery and identification (21, 22), creating what is now called “proteomics.”

A high throughput proteomic analysis system for prostate cancer using patient sera and plasma will be developed for this study. The methodologies/proteomic platforms to be used will be those that are a part of the NCI supported “Clinical Proteomic Technologies for Cancer program”.

In essence, these technologies develop spectra of individual proteins or peptides which correspond to the mass dependent time-of-flight to the detector. Resulting protein patterns will then be analyzed as clusters or groupings that are similar or not similar. A set of known “training” samples will be used to segregate the data into two types of clusters: those containing samples from patients known to have hormone refractory prostate cancer (n=100) and clusters containing samples from patients with hormone sensitive prostate cancer (n=100). After “training” a computer algorithm, the pattern of an unknown sample will be diagnostically classified by its similarity to the diseased or unaffected clusters found in the training set. Training the computer will be done by means of computer-simulated Darwinian evolution in which the outcome is “survival of the fittest” subset of data in a sample. The algorithm starts by randomly selecting many proteomic patterns within the training data for analysis. Each chosen pattern is tested to see how well it can discriminate affected from unaffected individuals in the training set, by cluster analysis. Successful proteomic patterns are kept and recombined, whereas unsuccessful patterns are discarded. Ultimately, a best pattern emerges after many iterations by the algorithm. This pattern, which best segregates the training sets, is used to diagnostically classify unknown samples.

In summary, the plasma and serum samples that result from the clinical trial will be subjected to different proteomic platforms, and potential biomarkers will be identified by MS/MS or multiplex ELISA platforms. This approach will permit a comprehensive search for changes in polypeptide profiles that are present at the various stages of prostate cancer. The hypothesis to be tested is that there are proteins differentially translated from the genome in hormone sensitive prostate cancer, prostate cancer that has responded to hormonal therapy and hormone

refractory prostate cancer. This analysis will be performed by investigators with appropriate expertise under the direction of Dr. Christopher Sweeney.

The following definitions will be applied:

The “hormone sensitive” patients will be defined as patients who have met eligibility criteria. It is known that 90% of these patients will have a PSA response. Patients who do not respond (per Section [6.3](#)) to androgen ablation will be removed from the analysis.

“Prostate cancer that has responded to hormonal therapy” will be defined in patients with a PSA that has met PSA criteria for PSA response (per Section [6.3](#)) and is maintained at the 6 month mark from start of protocol therapy. In some cases, patients will have been on therapy for up to 12 months (120 day window for androgen ablation prior to enrollment). Patients treated with androgen ablation alone will be analyzed separately and in combination with the patients who received chemotherapy.

Plasma and serum from patients with “hormone refractory prostate cancer” will be obtained from patients who have provided serum and plasma at time of hormone refractory disease (see Section [6.4.2](#) for definition).

To ensure reproducibility the following analyses will be performed:

All samples will be run in duplicate. A run-in pilot study on samples from 70 patients with HRPC has been conducted at Indiana University and the optimized conditions from these experiments will be applied to the samples from this protocol. A normal serum control sample will be added to one spot on each chip to serve as quality control for chip integrity, process integrity, and mass spectrometer function. All samples and controls will be added randomly to the chips. Samples of replicates will be run in separate batches to assess inter-assay variability. Samples from different “disease states” (e.g. hormone sensitive and hormone refractory) will be intermingled to avoid assay batch effects.

Planned Analysis - Training Set/Test-set Approach

Samples from the Hoosier Cancer Research Network (HCRN) trial “A phase III, randomized, double-blind, placebo-controlled trial evaluating the ability of risedronate to prevent skeletal related events in patients with metastatic prostate cancer commencing hormonal therapy” as well as the first 30 patients from E3805 will serve as the training set. Samples for the HCRN study have been collected at the same time points as E3805. Classifiers will be completely specified based on data from this study. There are approximately 60 patients from the HCRN study and will be combined with the first 40 patients from E3805 to develop the “training set” and the second 100 patients from E3805 to form the “test set”. Using the test set of size 100, overall accuracy of the classifier can be estimated to within approximately +/- 10%.

11.1.1 Sample Submission

Plasma and serum aliquots submitted as outlined in Section [10](#) will be used for this study. No additional samples are requested.

11.2 Germline Genetic Analysis

11.2.1 Genome Wide Association Study (GWAS)

This study seeks to develop preliminary data for the conduct of a genome wide association study (GWAS). A number of prior studies support the hypothesis that there are germ-line determinants of ADT. Using a candidate approach, Dr. Sweeney's group at Dana Farber Cancer Institute (DFCI) has shown that SNPs of genes associated with androgen synthesis, transport and metabolism impact duration of disease control with ADT.^{2,3} The top results from this study will require further validation in independent datasets.

As part of the Gelb Center at DFCI, Dr. Sweeney's group isolated DNA from 950 prostate cancer patients who initiated ADT for advanced disease and whose clinical outcomes are richly annotated, with a median follow-up of approximately six years – approximately 450 of these patients commenced ADT for radiographically evident metastatic disease (akin to E3805 patient population). This complementary dataset enables sufficient statistical power to validate findings from the GWAS. Dr. Sweeney's group will use the E3805 GWAS as preliminary data to perform the validation studies to conclusively identify inherited genetic variants associated with ADT response. The data will also be made available to other ECOG-ACRIN investigators with well annotated germ-line DNA repositories (e.g. Mayo Clinic).

Pairing the GWAS data with an analysis of the patient's corresponding tumor DNA and blood borne proteins and steroids will facilitate studies that will go beyond "association". Namely, we will be able to assess the impact of SNPs on the tumor compartment by determining protein or gene expression levels of related proteins from the diagnostic prostate biopsy or prostatectomy specimen. Moreover, if SNPs are found in (for example) androgen synthesis genes or the genes in the IGF pathway, we can assess the relevant steroid or IGF related protein level at the time of commencing ADT or at 6 months when responding or at time of progression. Namely, blood has been drawn at each of these time points.

It is recognized GWAS studies require large numbers of cases in order to achieve adequate statistical power. As a result, there have not been any definitive GWAS studies to assess the important clinical trait of ADT response because of the difficulty of assembling annotated cohorts of adequate size. Given the fact GWAS have revolutionized our ability to define the genetic basis of specific human traits and we now have the E3805 cohort and access to validation cohorts, we can now comprehensively interrogate the genome for inherited markers associated with ADT response.

- 11.2.2 In addition to analyzing the blood borne protein, an analysis of the germline DNA may also provide insight into the causes of prostate cancer and outcomes from treatment. We acknowledge that analyses of genetic polymorphisms will initially be exploratory. However, the potential value of obtaining the DNA and performing the analyses will provide the basis for further directed research. Moreover, this well powered prospective trial provides the platform to serve as a validation set for other findings. Dr Sweeney will oversee this work

and will collaborate with investigators with the appropriate expertise in this endeavor (34-38). The same precautions for protecting the anonymity of the patients and obtaining consent to perform the studies will be adhered to as those described for the proteomic analysis. We will obtain ethnicity information on all patients as polymorphisms often differ between ethnic groups. Two examples of the analyses that can be performed are the following:

1. Pharmacogenetic analysis of drug metabolism and transport genes

Cytochrome p450 3A4 and mdr genes metabolize and transport chemotherapeutics such as docetaxel respectively. As such variants of these genes may predict for altered efficacy and toxicity. Preliminary data from a Hoosier Cancer Research Network trial assessing two docetaxel based regimens for hormone refractory prostate cancer found that patients with the more functional ABCG2 (breast cancer resistance protein – BCRP) gene with C/C at position 421 have a lower chance of being alive beyond 15 months (27% of 44 patients) compared with those with the less functional transporter (C/A). In the later group, 4 of 6 patients were alive beyond 15 months ($p=0.05$). It is therefore hypothesized that, the presence of a less functional germline transporter predicts for less efflux of cytotoxic drugs from cancer cells and better survival. It should be recognized this was from an analysis of only 52 patients. Therefore a study such as E3805 with a larger number of patients is needed to confirm or refute the significance of this finding. The C/A variant is found in about 25% of Caucasians. Therefore, approximately 70 patients (25% of 270) treated with docetaxel when commencing hormonal therapy will have this variant. It is hypothesized that this group will have a longer time to hormone refractory disease than those with the C/C genotype (approximately 200 patients) as the latter group will have a more effective drug transporter to remove docetaxel from the tumor. The time to progression of patients with C/A and C/C genotypes treated with androgen ablation alone will be analyzed and compared with their counterparts on the chemohormonal therapy arm. An example of the statistical power that will be available to address pharmacogenetic questions such as the one detailed with the ABCG2 gene is the following. Assume that the C/A genotype occurs in approximately 25% of patients and it confers a better overall survival

2. Analysis of genetic polymorphisms that may alter the activity of enzymes involved in activation or deactivation of steroid hormones

The rationale for this is the following: The development of prostate cancer is possibly modulated by steroid hormones and many steroids and environmental carcinogens are subject to cytochrome P450 mediated metabolism which can generate reactive metabolites and may promote tumor initiation. Polymorphisms in the enzymes that are specifically involved in the metabolism of steroids may therefore be a specific risk factor for this disease. Some studies have suggested that this may in fact be the case (26-33). We will access the DNA of

Rev. 1/15

patients enrolled onto this trial and determine the frequency of polymorphisms of enzymes that are possibly involved in the genesis of prostate cancer. This will then be compared with frequency of these polymorphisms that will be identified from a screened population (e.g. samples and analyses can be obtained from a screening study that is being conducted at Indiana University). The analysis in the screening study will employ a case-control design. The frequency of polymorphisms in E3805 will then be compared informally with the results from the screening study. The demographics and ethnicity of patients from both E3805 and the screening study will be known and allow investigators to investigate the generalizability of the data from the two studies. One published example of a polymorphism of interest is an analysis in a Japanese population of the cytochrome p450 1B1 gene. This gene encodes for an enzyme involved in the hydroxylation of steroid hormones. The odds ratio for developing prostate cancer if the genotype T/T at codon 119 was 4.02 compared to the reference genotype of G/G (95% confidence interval: 1.73-9.38 - $P < 0.001$). Validating the frequency and significance of this polymorphism in a study of patients with metastatic disease and in what we expect to be predominately Caucasian population is required. Genes involved in the metabolism of steroid hormones have been reported to impact efficacy of ADT and E3805 has the potential to serve not only as a discovery but also a validation set.

This analysis will be performed with collaborators with appropriate expertise under the direction of Dr. Christopher Sweeney. ival for patients receiving docetaxel. With genotype results from 270 patients receiving docetaxel, there will be approximately 90% power to detect a hazard ratio of 1.8 when comparing overall survival between C/C and C/A groups using a two-sided 0.05 level logrank test and assuming a median overall survival of 32 months in the docetaxel arm and accrual over 45 months with 36 months additional follow-up.

11.2.3 Sample Submission

DNA will be extracted and analyzed from the lavender top tube blood samples submitted as outlined in Section [10](#). No additional samples are requested.

11.3 Tumor Tissue Analysis.

This correlative study is administratively withdrawn effective March 1, 2016.

Tumor tissue obtained in a standardized fashion with clinical data from patients with metastatic disease is limited. E3805 provides a unique opportunity to obtain tissue tumor from this unique population. Moreover, technologies have advanced to allow extraction of DNA, RNA, micro-RNA and analyses of other tumor and tumor-stroma components including proteins from formalin fixed paraffin embedded (FFPE) tissue. An example of how this tissue can be studied in the following. Specifically, it has been noted that the expression of nuclear factor kappa B has been reported to be over-expressed in organ confined prostate cancer (39). However, the impact of NFkB activation on prognosis is

unknown at this time. CXCR4 and Manganese superoxide dismutase are proteins under the control of nuclear factor kappa B and are associated with metastasis and avoidance of apoptosis respectively. Other proteins of interest under control of NFkB that will be analyzed include TRAF-1, Bcl-XL, and cIAP2, The amount and frequency of expression of these genes and proteins as well as BCL-2 will be analyzed in the samples using immunohistochemistry and multiplex mRNA platforms from patients on this trial (with metastatic disease) and compared with samples from patients who never developed metastatic disease and will also be correlated with nuclear factor kappa B expression. This analysis will be performed under the direction of Dr. Christopher Sweeney with collaborators with the requisite expertise.

11.3.1 Sample Submission

The prostate cancer pathology or appropriate slides that were submitted as outlined in Section [10](#) will be used for this study. No additional samples are requested.

12. Records to Be Kept

Please refer to the E3805 Forms Packet for the forms submission schedule and copies of all forms. The E3805 Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (<http://www.ecog.org>). Forms must be submitted to the ECOG-ACRIN Operations Office – Boston, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA).

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

14. References

1. Jemal A, Tiwari RC, Murray T, et al: Cancer statistics, 2004. *CA Cancer J Clin* 54:8-29, 2004
2. Pound CR, Partin AW, Eisenberger MA, et al: Natural history of progression after PSA elevation following radical prostatectomy. *Jama* 281:1591-7., 1999
3. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. *Lancet* 355:1491-8, 2000
4. Eisenberger MA, Blumenstein BA, Crawford ED, et al: Bilateral orchiectomy with or without flutamide for metastatic prostate cancer [see comments]. *N Engl J Med* 339:1036-42, 1998
5. Crawford ED, Eisenberger MA, McLeod DG, et al: A controlled trial of leuprolide with and without flutamide in prostatic carcinoma [published erratum appears in *N Engl J Med* 1989 Nov 16;321(20):1420]. *N Engl J Med* 321:419-24, 1989
6. Serafini AN, Houston SJ, Resche I, et al: Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. *J Clin Oncol* 16:1574-81, 1998
7. Myers C, Cooper M, Stein C, et al: Suramin: a novel growth factor antagonist with activity in hormone-refractory metastatic prostate cancer [see comments]. *J Clin Oncol* 10:881-9, 1992
8. Tannock I, Gospodarowicz M, Meakin W, et al: Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. *J Clin Oncol* 7:590-7, 1989
9. Tannock IF, Osoba D, Stockler MR, et al: Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol* 14:1756-64, 1996
10. Kantoff PW, Halabi S, Conaway M, et al: Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. *J Clin Oncol* 17:2506-13, 1999

11. Petrylak DP, Tangen CM, Hussain MH, et al: Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 351:1513-20, 2004
12. Tannock IF, de Wit R, Berry WR, et al: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 351:1502-12, 2004
13. Haldar S, Basu A, Croce CM: Bcl2 is the guardian of microtubule integrity. *Cancer Res* 57:229-33, 1997
14. Zellweger T, Ninck C, Bloch M, et al: Expression patterns of potential therapeutic targets in prostate cancer. *Int J Cancer* 113:619-628, 2004
15. Bruckheimer EM, Kyprianou N: Bcl-2 antagonizes the combined apoptotic effect of transforming growth factor-beta and dihydrotestosterone in prostate cancer cells. *Prostate* 53:133-42, 2002
16. Shi XB, Ma AH, Tepper CG, et al: Molecular alterations associated with LNCaP cell progression to androgen independence. *Prostate* 60:257-71, 2004
17. Rothermund CA, Gopalakrishnan VK, Vishwanatha JK: Androgen signaling and post-transcriptional downregulation of Bcl-2 in androgen-unresponsive prostate cancer. *Prostate Cancer Prostatic Dis* 7:158-64, 2004
18. Gleave ME, Miyake H, Goldie J, et al: Targeting bcl-2 gene to delay androgen-independent progression and enhance chemosensitivity in prostate cancer using antisense bcl-2 oligodeoxynucleotides. *Urology* 54:36-46, 1999
19. Beer TM, Garzotto M, Henner WD, et al: Multiple cycles of intermittent chemotherapy in metastatic androgen-independent prostate cancer. *Br J Cancer* 91:1425-7, 2004
20. O'Farrel PH: High resolution two-dimensional gel electrophoresis of proteins. *J. Biol. Chem.* 250 250: 4007:4007, 1975
21. Carr SA, R.S.: *Overview of Peptide and Protein Analysis by Mass Spectrometry.* New York, John Wiley and Sons Inc, 1998
22. Patterson SD: *Protein Identification and Characterization by Mass Spectrometry.* New York, J. Wiley and Sons Inc.,, 1998
23. Wright GL, Cazares, L.H., Leung, S.M., Masim, S., Adam, B-L., Yip, T-T Schellhammer, P.D., Gong, L., and Vlahou A: ProteinChip Surface enhanced laser desorption/ionization mass spectrometry; A novel protein biochip technology for detection of prostate cancer biomarkers in complex protein mixtures. *Prostate Cancer and Prostate Diseases* 2:264-276, 1999
24. Malkas L: DNA replication machinery of the mammalian cell. *J. Cell. Biochem. Suppl.* 30/31:18-29., 1998
25. Petricoin EF, Ardekani AM, Hitt BA, et al: Use of proteomic patterns in serum to identify ovarian cancer. *Lancet* 359:572-7, 2002
26. Tanaka Y, Sasaki M, Kaneuchi M, et al: Polymorphisms of the CYP1B1 gene have higher risk for prostate cancer. *Biochem Biophys Res Commun* 296:820-6, 2002
27. Friedberg T: Cytochrome P450 polymorphisms as risk factors for steroid hormone-related cancers. *Am J Pharmacogenomics* 1:83-91, 2001
28. Allen NE, Forrest MS, Key TJ: The association between polymorphisms in the CYP17 and 5alpha-reductase (SRD5A2) genes and serum androgen concentrations in men. *Cancer Epidemiol Biomarkers Prev* 10:185-9, 2001

29. Murata M, Watanabe M, Yamanaka M, et al: Genetic polymorphisms in cytochrome P450 (CYP) 1A1, CYP1A2, CYP2E1, glutathione S-transferase (GST) M1 and GSTT1 and susceptibility to prostate cancer in the Japanese population. *Cancer Lett* 165:171-7, 2001
30. Wadelius M, Autrup JL, Stubbins MJ, et al: Polymorphisms in NAT2, CYP2D6, CYP2C19 and GSTP1 and their association with prostate cancer. *Pharmacogenetics* 9:333-40, 1999
31. Lunn RM, Bell DA, Mohler JL, et al: Prostate cancer risk and polymorphism in 17 hydroxylase (CYP17) and steroid reductase (SRD5A2). *Carcinogenesis* 20:1727-31, 1999
32. Westlind A, Lofberg L, Tindberg N, et al: Interindividual differences in hepatic expression of CYP3A4: relationship to genetic polymorphism in the 5'-upstream regulatory region. *Biochem Biophys Res Commun* 259:201-5, 1999
33. Febbo PG, Kantoff PW, Giovannucci E, et al: Debrisoquine hydroxylase (CYP2D6) and prostate cancer. *Cancer Epidemiol Biomarkers Prev* 7:1075-8, 1998
34. Desta Z, Zhao X, Shin JG, et al: Clinical significance of the cytochrome P450 2C19 genetic polymorphism. *Clin Pharmacokinet* 41:913-58, 2002
35. Shon JH, Yoon YR, Kim KA, et al: Effects of CYP2C19 and CYP2C9 genetic polymorphisms on the disposition of and blood glucose lowering response to tolbutamide in humans. *Pharmacogenetics* 12:111-9, 2002
36. Tanus-Santos JE, Desai M, Flockhart DA: Effects of ethnicity on the distribution of clinically relevant endothelial nitric oxide variants. *Pharmacogenetics* 11:719-25, 2001
37. Flockhart DA, Oesterheld JR: Cytochrome P450-mediated drug interactions. *Child Adolesc Psychiatr Clin N Am* 9:43-76, 2000
38. Xie HG, Stein CM, Kim RB, et al: Allelic, genotypic and phenotypic distributions of S-mephenytoin 4'-hydroxylase (CYP2C19) in healthy Caucasian populations of European descent throughout the world. *Pharmacogenetics* 9:539-49, 1999
39. Sweeney C, Li L, Shanmugam R, et al: Nuclear factor-Kappa B is constitutively activated in prostate cancer in vitro and is over expressed in prostatic intraepithelial neoplasia and adenocarcinoma of the prostate. *Clin Cancer Res* 10:5501-7, 2004.
40. Cella D, Peterman A, Hudgens S, Webster K, & Socinski MA. (2003). Measuring the side effects of taxane therapy in oncology: The Functional Assessment of Cancer Therapy – Taxane (FACT-Taxane). *Cancer*. 98(4):822-31.
41. Esper, P, Fei, M., Chodak, G., Sinner, M., Cella, D. & Pienta, K. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Adult Urology*, 50:920, 1997.
42. Levine, AJ. p53, the cellular gatekeeper for growth and cell division. *Cell*, 88:323, 1997.
43. Smith DC, Esper P, Strawderman M, Redman B, & Pienta KJ. Phase II trial of oral estramustine, oral etoposide and intravenous plactaxel in hormone-refractory prostate cancer. *Journal of Clinical Oncology*, 17: 1664, 1999.

44. Stockler MR, Osaba D, Corey P, Goodwin PJ, & Tannock I. Convergent discriminative, and predictive validity of the prostate cancer specific quality of life instrument (PROSQOLI): assessment and comparison with analogous scales from the EORTC QLQ-C30 and a trial-specific module. *Clinical Epidemiology* 52:653, 1999.
45. American Society of Health –System Pharmacists. Hospital formulary service drug information, 2000.
46. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, & Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clinical Infectious Diseases* 18: S79, 1994.
47. Cella D. The functional assessment of cancer therapy-anemia (FACT-An) scale: A new tool for the assessment of outcomes in cancer anemia and fatigue. *Seminars in Hematology* 34:13, 1997.
48. Yellen SB, Cella DF, Webster K, Blendowski C, & Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *Journal of Pain and Symptom Management* 13: 63, 1997.
49. Lin C, & Ward SE. Patient related barriers to cancer pain management. *Cancer Nursing* 18: 16, 1995.
50. Daut R, Cleeland CS, Flanery R. Development of the Wisconsin Brief Pain Inventory to assess pain in cancer and other diseases. *Pain* 17:197, 1982.
51. Scher et al *J Clin Oncol* 26: 1148-119; 2008.

Rev. 2/10

**CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for
Extensive Disease Prostate Cancer**

Appendix I

**Informed Consent Template for Cancer Treatment Trials (English Language)
[Deleted in Addendum #6]**

**INFORMED CONSENT INTENTIONALLY REMOVED FROM
PROTOCOL DOCUMENT**

**Appendix I was removed from the protocol document in Addendum #6 and is posted as a
separate document on the ECOG website. This was removed from the protocol to comply
with NCI formatting guidelines.**

**CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for
Extensive Disease Prostate Cancer**

Appendix II

Pathology Submission Guidelines

The following items are included in Appendix II:

1. Guidelines for Submission of Pathology Materials
(instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. List of Required Materials for E3805
4. ECOG-ACRIN Generic Specimen Submission Form (#2981)

Rev. 1/15

Rev. 1/15

Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)
- ECOG-ACRIN Generic Specimen Submission Form (#2981)

Instructions:

1. Place the Patient ID label provided by the ECOG-ACRIN Operations Office – Boston in Part A of the Pathology Material Submission Form.

If a label is not available, **TYPE or PRINT** the following information in **Part A** of the form:

- Patient's name (last, first)
 - Protocol number
 - Protocol case number (the patient's ECOG-ACRIN sequence number; for intergroup studies, include both the ECOG-ACRIN and other group's sequence numbers)
 - Patient's hospital number
 - Institution
 - Affiliate (if appropriate)
2. Complete blank areas of the pathologist's instructional memo, and forward it, along with the List of Required Material and the Pathology Material Submission Form, to the appropriate pathologist.
 3. The pathologist should return to you the required pathologic samples and surgical pathology reports, along with the completed. If any other reports are required, they should be obtained from the appropriate department at this time.
 4. Keep a copy of the ECOG-ACRIN Generic Specimen Submission Form (#2981) for your records (the original should be sent to the ECOG-ACRIN CBPF).
 5. Double check that ALL required forms, reports, and pathology samples are included in the package to send to the Central Biorepository and Pathology Facility (see appropriate List of Required Material).

Pathology specimens submitted for a patient WILL NOT be processed by the Central Biorepository and Pathology Facility until all necessary items are received.

6. Mail pathology materials to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030

Rev. 2/07

If you have any questions concerning the above instructions, or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility at Tel: 1-844-744-2420 or Email: eacbpf@mdanderson.org.

List of Required Material

| |
|--|
| E3805 CHARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease Prostate Cancer |
|--|

Pre-Treatment

Rev. 1/15

1. ECOG-ACRIN Generic Specimen Submission Form (#2981)
2. Institutional pathology report (***must be included with EVERY pathology submission***).
3. Study-specific On-Study Form in addition to the form sent to the ECOG-ACRIN Operations Office – Boston.
4. Requested pathology materials:

Rev. 8/09

- One tumor block. If a tumor block is not available, five (5) unstained positively charged slides and one H&E slide may be substituted.

NOTE: Blocks are available for return upon written request for purposes of patient management. However, since blocks are being used for laboratory studies, in some cases the material may be depleted and therefore, the block may not be available for return.

Rev. 1/15



Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD
Group Co-Chairs

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: Submission of Pathology Materials for E3805

The patient named on the attached ECOG-ACRIN Generic Specimen Submission Form (#2981) has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for **laboratory studies**.

Please complete PART B of the Submission Form. Keep a copy for your own records, and return the completed Submission Form, the surgical pathology report(s), the slides and/or blocks, and any other required material (see attached List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG-ACRIN Central Biorepository and Pathology Facility.

Blocks and slides submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies. Paraffin blocks will be returned for purposes of patient management upon written request.

Please note: Since blocks are being used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.

If you have any questions regarding this request, please feel free to contact the Central Biorepository and Pathology Facility at Tel: 1-844-744-2420 OR EMAIL: eacbpf@mdanderson.org.

The ECOG-ACRIN CRA at your institution is:

Name: _____

Address: _____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Page 1 of 1

Institution Instructions: This form is to be completed and submitted with **all specimens ONLY** if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

| Required fields for all samples | | | | Additional fields for tissue submissions | | | | Completed by Receiving Lab |
|---|----------|-----------------------------------|--|--|------------------|--|----------------------|----------------------------|
| Protocol Specified Timepoint: | | | | | | | | |
| Sample Type (fluid or fresh tissue, include collection tube type) | Quantity | Collection Date and Time 24 HR | | Surgical or Sample ID | Anatomic Site | Disease Status (e.g., primary, mets, normal) | Stain or Fixative | Lab ID |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

| Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required. | | | | | |
|---|-----------------------------|--------------------------|----------------------------------|---------------------|---------------|
| Leukemia/Myeloma Studies: | Diagnosis | Intended Treatment Trial | Peripheral WBC Count (x1000) | Peripheral Blasts % | Lymphocytes % |
| | | | | | |
| Study Drug Information: | Therapy Drug Name | Date Drug Administered | Start Time 24 HR | Stop Time 24HR | |
| | | | | | |
| Caloric Intake: | Date of Last Caloric Intake | | Time of Last Caloric Intake 24HR | | |
| | | | | | |

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease Prostate Cancer

Appendix III

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at <http://www.ecog.org>. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME]

[DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important clinical program. Programs like this offer a chance to get the best care while helping us make better care available for all patients. Many questions remain unanswered in cancer. With the help of people like you who participate in these programs, we will achieve our goal of effectively treating and ultimately curing cancer.

We believe this program will provide you with high quality, thorough care. Your physician and research staff will maintain very close contact with you. This is important to allow your physician to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of **[INSTITUTION]** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease Prostate Cancer

Rev. 2/07

Appendix IV

Cancer Trials Support Unit (CTSU) Participation Procedures

REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Rev. 6/14

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site at <http://members.ctsu.org>

All forms and documents associated with this study can be downloaded from the E3805 Web page on the CTSU registered member Web site (<https://members.ctsu.org>). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as ‘approved’ in the CTSU RSS.

Requirements for E3805 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Prestudy requirements for patient enrollment on E3805:

- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms
- All baseline laboratory tests and prestudy evaluations performed within the time period specified in the protocol.
- Patient completes baseline QOL forms prior to treatment start.

CTSU Procedures for Patient Enrollment

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.

2. Complete the following forms:
 - CTSU Patient Enrollment Transmittal Form
 - E3805 Eligibility Checklist
3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 8:00 p.m., Mon-Fri, Eastern Time (excluding holidays). The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.
4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the ECOG-ACRIN. The CTSU registrar will access the ECOG-ACRIN's on-line registration system, to obtain and assignment of a treatment arm and a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.
 - Protocol treatment should start within five working days after randomization.

DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the E3805 Web page located on the CTSU registered member Web site (<https://members.ctsu.org>). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.
2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the ECOG-ACRIN [refer to contacts table] unless an alternate location is specified in the protocol. Do not send study data to the CTSU. A completed CTSU-ECOG-ACRIN coversheet should accompany all data submissions.
3. The ECOG-ACRIN Operations Office – Boston will mail query notices and delinquency reports directly to the site for reconciliation. Please send query responses and delinquent data to the ECOG-ACRIN Operations Office – Boston and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the ECOG-ACRIN Operations Office – Boston.

SPECIAL MATERIALS OR SUBSTUDIES

NOTE: ECOG-ACRIN requires that all biological samples submitted from patients participating in this trial be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See Section [10.4](#).

1. Pathology Submission (Protocol Section [10.0](#))
 - Submission of pathologic material for correlative studies is optional.
 - Collect, prepare, and submit specimens as outlined in the protocol.
 - Do not send specimens, supporting clinical reports, or transmittals to the CTSU.
2. Specimen collection for correlatives (Protocol Section [11.0](#))
 - Participation in the correlative studies is optional and requires patient consent.

Rev.9/16

- Kits are available for the collection of samples. Complete the Kit Order Form ([Appendix VI](#)) and fax to Mayan Howard and Michael Nunley at (317) 921-2053.
 - Collect, prepare, and submit specimens as outlined in the protocol.
 - Do not send specimens, supporting clinical reports, or transmittals to the CTSU.
3. Quality of Life Substudies (Protocol Section [5.1](#))
- Submit completed forms as outlined in the protocol.

SERIOUS ADVERSE EVENT (AE) REPORTING (Section [5.3](#))

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.
2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP's Adverse Event Reporting System (CTEP-AERS) from either the Adverse Events tab of the CTSU member homepage (<https://members.ctsu.org>) or by selecting Adverse Event Reporting Forms from the document center drop down list on the E3805 Web page.
3. Do not send adverse event reports to the CTSU.
4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu of CTEP-AERS. Submit the completed form and supporting documentation as outlined in the protocol.

DRUG PROCUREMENT (Section [8.0](#))

Investigational agent: Docetaxel (This drug is a commercially marketed drug, however, when used as directed by this protocol, docetaxel is classified as an "unapproved use of an approved agent" and, by definition, considered as an investigational agent. However, while it is not an indication currently approved by the FDA, the use of docetaxel in this protocol is exempt from the requirements of an IND as described under Title 21 CFR 312.2(b).)

Docetaxel (Taxotere®) is available and distributed free of charge from Sanofi-Aventis Pharmaceuticals. After patient randomization, a supply of docetaxel may be obtained. Investigators must fax a signed and completed "E3805 Clinical Supplies Shipping Form" ([Appendix VI](#)) to the ECOG-ACRIN Operations Office – Boston, ATTN: Drug Team at 617-632-2063. Do not send drug requests directly to Sanofi-Aventis Pharmaceuticals. Allow 4-5 business days for receipt of the drug. See Section [8.0](#) for further drug information and re-orders.

Commercial agents: LHRH agonists (such as leuprolide, goserelin, triptorelin); Antiandrogens (flutamide and bicalutamide)

1. Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in Section [8.0](#) of the protocol.
2. You may navigate to the drug forms by selecting Pharmacy Forms from the document center drop down list on the E3805 Web page.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. (e.g., NSABP members may only request credit for protocols pertaining to breast or colorectal cancers). Registrations to protocols for other disease sites may still take place through CTSU without receiving credit for your NSABP activities. Per capita reimbursement will be issued directly from CTSU.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data Update System (CDUS) 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. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.

CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease Prostate Cancer

Appendix V

**Treatment of Hypersensitivity Reactions
MANAGEMENT OF ACUTE HYPERSENSITIVITY**

| Severity of Symptoms | Treatment Guidelines |
|--|---|
| <p>Mild symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash</p> | <ul style="list-style-type: none"> • consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient • then, complete docetaxel infusion at the initial planned rate |
| <p>Moderate symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mm Hg</p> | <ul style="list-style-type: none"> • interrupt docetaxel infusion • give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor patient until resolution of symptoms • resume docetaxel infusion after recovery of symptoms; depending on the physician's assessment of the patient, docetaxel infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate, (e.g. <i>infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, then finally, resume at the 1-h infusion rate</i>) • depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the next cycle of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hour infusion, (e.g. <i>infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, and finally, administer at the 1-h infusion rate</i>) |
| <p>Severe symptoms: any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80mm Hg, angioedema</p> | <ul style="list-style-type: none"> • immediately discontinue docetaxel infusion • give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor patient until resolution of symptoms • the same treatment guidelines outlined under moderate symptoms (i.e. the third and fourth bullets) should be followed. |
| <p>Anaphylaxis (NCI grade 4 reaction)</p> | <ul style="list-style-type: none"> • NO FURTHER STUDY DRUG THERAPY |

CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease Prostate Cancer

Rev.9/16

Appendix VI

E3805 Collection and Shipping Kit Order Form

NOTE: As of March 31, 2016 collection of blood samples is closed.

Upon institutional IRB approval complete and fax this form as indicated below. A minimum of 5 working days notice is required. Kits will NOT be shipped overnight unless clearly stated on this form that it is needed within 24 hours **due to patient enrollment** only.

Provided sample collection kits will contain all items needed including: blood tubes, cryovials, labels and Thermosafe shippers. It is important that you use only the collection kits and Thermosafe shippers provided by the Hoosier Cancer Research Network.

Rev. 1/15

TODAYS DATE: _____ Date of Institutional IRB approval: _____

Date Kits are Needed: _____ (Provide 5 working days notice)

Kits Needed:

| TYPE | HOW MANY NEEDED? | Comments |
|--|------------------|----------|
| Baseline Collection Kits | | |
| Week 24 Collection Kits | | |
| Time of Progression Kits | | |
| Thermosafe Shippers (2 sent per shipment) | | |

*Comments: _____

Kits are to be shipped to:

Institution Name: _____

Institution Contact: _____

Phone number for contact: _____

E-mail for contact: _____

Institution Address: _____

FAX Completed form to Mayan Howard and Michael Nunley at (317) 921-2053.

Questions are to be directed to the Mayan Howard and Michael Nunley by email at mhoward@hoosiercancer.org and mnunley@hoosiercancer.org or by calling (317) 921-2050.

CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease Prostate Cancer

Appendix VII

**E3805 Clinical Supplies Shipping Form
To Investigator Only**

SECTION 1 – TO BE COMPLETED BY SITE

Requested By:

Mail stop :

Telephone:

Fax :

Protocol No. : E3805

IND/CTX No. : N/A

Ship to the attention of :

Investigator No.:

Address :

Investigator Name:

Telephone:

Fax :

SECTION 2 All line items MUST be completed by the ECOG-ACRIN OPERATIONS OFFICE – BOSTON DRUG TEAM

- a) Investigator shipments: The regulatory requirements are fulfilled at the clinical study center according to valid SOPs
- b) IND studies: Required documents (e.g. protocols. 1572, CV) have been provided to the Regulatory Representative for IND submission/maintenance Not applicable
- c) Initial shipment Reshipment

Requestor Name and Title :

Date :

Signature :

REQUESTED SHIP DATE : TO BE COMPLETED BY SITE

Financial Account No. N/A

ECOG-ACRIN Patient Sequence Numbers:

We are pleased to send you the following Investigational Products: COMPLETED BY SA

| Number of Patient kits or quantity of bulk drug product | Treatment Period (if applicable) | Product Name/ Strength/ Form | PR or Lot Number | Use by Date |
|---|----------------------------------|------------------------------|------------------|-------------|
| | | | | |
| | | | | |
| | | | | |

STORAGE CONDITIONS :

PR Number:

Sanofi-aventis Tracking N° :

Number of containers used for shipment:

Carrier/AWB Number :

Invoice

Code Breaks Number of set(s) :

Release Certificate and Certificate of Conformance :

Additional document:

Certificate(s) of Analysis

Randomization list

Comments :

Packed by :

Checked by :

Actual Shipment Date :

ACKNOWLEDGEMENT OF RECEIPT – TO BE COMPLETED BY SITE

Please acknowledge receipt of the shipment by checking the contents and signing approval below:

Number of containers received:

Contents received intact: Yes No ; If No, please explain: _____

Date received: _____ Signature : _____ Print Name: _____

Please fax acknowledgement of receipt to Aventis Attention: Debra Dawson at fax No. 908-243-7745
(local contact)