ECOG-ACRIN cancer research group
Reshaping the future of patient care

EA8153

# Cabazitaxel with Abiraterone versus Abiraterone alone Randomized Trial for Extensive Disease following Docetaxel: the CHAARTED2 Trial


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**Version Date:** September 17, 2021


***STUDY PARTICIPANTS***

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**NRG** / NRG Oncology
**SWOG** / SWOG

***ACTIVATION DATE***

February 8, 2018

Addendum #1
Addendum #2
Addendum #3
Rev. Add4 Addendum #4

***NCTN GROUP STUDY CHAMPIONS***

**ALLIANCE:** Yousef Zakharia, M.D.
**SWOG:** Paul Corn, M.D., Ph.D.

| Agents | IND# | NSC# | Supply |
|---|---|---|---|
| Abiraterone acetate | IND Exempt Study | 748121 | Commercially Available |
| Cabazitaxel | | 794609 | Genzyme |
| Prednisone | | 10023 | Commercially Available |

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## CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION

| **For regulatory requirements:** | **For patient enrollments:** | **For study data submission:** |
|---|---|---|
| Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.<br>Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.)<br>Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.<br>Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance. | Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.<br>Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com. | Data collection for this study will be done through Medidata Rave and the ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO) system. Please see the data submission section of the protocol for further instructions.<br>Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions. |
| The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. | | |
| **For clinical questions (i.e., patient eligibility or treatment-related)** Contact the Study PI of the Coordinating Group. | | |
| **For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission)** contact the CTSU Help Desk by phone or e-mail:<br>CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative. | | |
| **The CTSU Web site is located at** https://www.ctsu.org | | |

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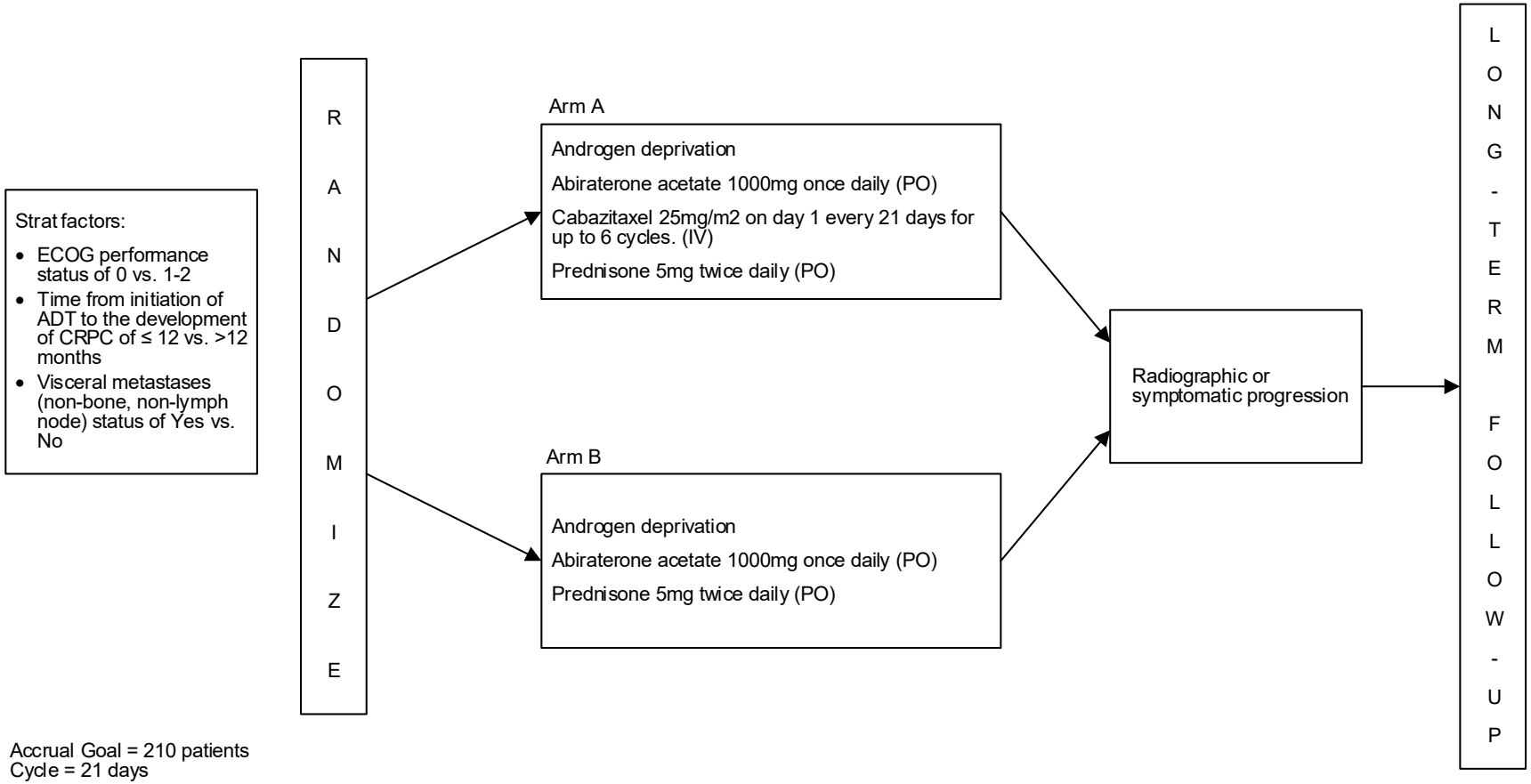
## Schema




Accrual Goal = 210 patients
Cycle = 21 days

1. All patients will continue androgen depravation as per standard of care.
2. All patients will receive Prednisone 5mg twice daily
3. Randomization 1:1 between the two arms

# 1. Introduction

## 1.1 Background

Prostate cancer is the most common cancer diagnosis and the second cancer-leading cause of death in men, with a 2016 estimate of 180,890 new cases and 26,120 deaths in the United States [1]. For patients with localized disease, treatment options for definitive therapy include surgery and/or radiation therapy. Approximately 1/3 of these men will experience disease recurrence as evidenced by a rise in their serum PSA [2]. While some men may still be cured with salvage therapies, most will eventually develop metastatic disease [3]. Ever since the critical role of androgens in stimulating prostate cancer growth was established [4], androgen deprivation therapy (ADT) with either surgical or medical castration remains the primary approach to the treatment of hormone-sensitive prostate cancer (HSPC). Although most men will initially respond to ADT [5], all patients will eventually develop castrate-resistant prostate cancer (CRPC), evidenced by increase in serum PSA, new clinical metastases, progression of existing metastases and/or worsening symptoms [6]. Over the last few years, several new agents have been added to our therapeutic armory [7]; however, the duration of response is limited, indicating the need for new treatment strategies that will further delay disease progression, prolong survival and improve quality of life.

The E3805 (CHAARTED) trial showed that the addition of 6 cycles of docetaxel to standard androgen deprivation therapy (ADT) significantly improved progression-free survival (PFS) and overall survival (OS) compared to standard ADT alone in men with metastatic hormone-sensitive prostate cancer [8]. The hypothesis behind that trial was that significant level of resistance to ADT is already present at the time of initial presentation in patients with metastatic disease and that this phenomenon is proportional to the extent of tumor burden; hence, decreasing burden may prolong benefit. In addition, a proportion of patients are too frail to receive docetaxel at the time of development of CRPC and as such they might miss the window to receive treatment with an active agent; thus, early treatment might confer additional benefit. Further, preclinical studies have shown a synergistic effect between ADT and taxanes, with significant delay in development of CRPC [9, 10] and as such combination of ADT and docetaxel can prolong survival. Seven hundred ninety previously untreated, hormone-naïve metastatic prostate cancer patients were randomly assigned to ADT plus docetaxel or to ADT alone. After a median follow-up of 28.9 months, there was a significant OS benefit of 13.6 months for the group that received chemohormonal therapy [median OS 57.6 vs. 44.0 months; HR 0.61 (0.47-0.80); p<0.001]. Further, the median time to clinical progression was significantly longer with chemohormonal therapy [33.0 vs. 19.8 months; HR 0.61 (0.50-0.75); p<0.001] and so the median time to CRPC development [20.2 vs. 11.7 months; HR 0.61 (0.51-0.72); p<0.001]. When patients were stratified based on tumor burden, the addition of docetaxel was found to significantly prolong the OS in the high-volume group [49.2 vs. 32.2 months, HR 0.60 (0.45-0.81); p<0.001]; however, despite a trend towards an improved survival in the low-volume group, that was not statistically significant at the time of follow-up. Based on those results, ADT in combination with docetaxel is considered the new standard of care for that patient population, as long as they are suitable for treatment with docetaxel chemotherapy.

In addition to the CHAARTED data, the STAMPEDE trial also showed a survival benefit from the early introduction of docetaxel chemotherapy in hormone-sensitive prostate cancer patients [11]. In that trial, patients were assigned to multiple regimens including ADT, docetaxel and zoledronic acid. The primary endpoint of OS was significantly improved for the patients treated with ADT plus docetaxel vs. patients that only received ADT (median OS 81 vs. 71 months, HR 0.78, 95% CI 0.66-0.93; p=0.006). In the subgroup analysis based on the presence or absence of metastatic disease, survival was significantly prolonged for patients with metastasis (median OS 60 vs. 45 months, HR 0.76, 95% CI 0.62-0.92; p=0.005); however, there was insufficient number of deaths in the group without radiographic metastasis to allow firm conclusions.

The above phase III trials have established the role of chemohormonal therapy for patients with newly diagnosed metastatic prostate cancer, at least in those patients with high-volume disease. However, it is unknown if the same strategy in the castration-resistant setting –especially in patients that have previously received docetaxel for ADT-naïve disease- will be of any value.

### 1.2 Rationale for selected approach and trial design

Despite the significant improvement in outcome by the addition of docetaxel to ADT, eventually all patients will develop castration-resistant disease. Current therapies in that setting include second-line androgen receptor (AR) signaling pathway inhibitors, chemotherapy, immunotherapy, radium-223, palliative radiation or supportive care. Upon development of castration-resistant disease, patients can receive sequential treatment with docetaxel rechallenge, cabazitaxel, sipuleucel-T, abiraterone acetate with prednisone, enzalutamide or radium-223. All the above agents have been approved for the treatment of metastatic CRPC patients based on studies that showed prolongation of survival; however, the clinical benefit of each of those therapies in patients that have previously received treatment with docetaxel in the hormone-naïve setting is unknown. Currently, the most commonly used agents in that setting are second-line androgen receptor signaling pathway inhibitors, such as abiraterone acetate. We hypothesize that a second course of chemohormonal therapy with cabazitaxel and abiraterone acetate will result in suppression of resistant clones to abiraterone acetate that are already present. This trial aims to evaluate whether the addition of 6 cycles of cabazitaxel to abiraterone acetate can prolong the PFS of patients with metastatic CRPC that have received first-line chemohormonal therapy with docetaxel for HSPC. In addition, even though this trial will be underpowered to confirm a prolongation in OS, it will seek preliminary data of OS benefit from the addition of cabazitaxel to abiraterone acetate. Finally, this trial will include exploratory biomarkers of disease resistance and response to therapy.

### 1.3 Therapeutic agents

Abiraterone acetate (Zytiga TM, Jannsen Biotech Inc, Horsham, PA) is an oral CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer. Two randomized phase III trials have shown survival benefit in the pre- and post-docetaxel setting, respectively. The COU-AA-301 double-blind placebo-controlled trial enrolled 1195 patients with metastatic CRPC that had previously received docetaxel chemotherapy for castration-resistant disease [12]. Patients received abiraterone acetate 1000 mg PO daily in combination with prednisone 5 mg PO twice daily

vs. placebo plus prednisone 5 mg PO twice daily. Median PFS was significantly improved in favor of the abiraterone acetate group vs. the placebo group (5.6 vs. 3.6 months; p<0.001). The median OS was also significantly prolonged for the patients that received abiraterone acetate with prednisone vs. placebo and prednisone [15.8 months (95% CI 14.8-17.0) vs. 11.2 months (10.4-13.1); HR 0.74, 95% CI 0.64-0.86; p<0.0001) [13]. Similarly, the COU-AA-302 double-blind placebo-controlled trial that examined the role of abiraterone acetate in combination with prednisone in chemotherapy-naïve patients showed an improvement in the median radiographic PFS in favor of abiraterone acetate (16.5 vs. 8.3 months; HR 0.53; 95% CI 0.45-0.62; p<0.001) [14]. Further, there was a significant survival benefit in favor of the abiraterone acetate arm as well [34.7 months (95% CI 32.7-36.8) vs. 30.3 months (28.7-33.3; HR 0.81, 95% CI 0.70-0.93; p=0.0033)] [15]. The most common side effects of abiraterone acetate in those trials were fluid retention, hypertension, hypokalemia and liver-function abnormalities. Based on those two studies abiraterone acetate in combination with prednisone was approved for the treatment of metastatic CRPC patients both before and after treatment with docetaxel.

In addition to the second-line AR signaling pathway inhibitors, chemotherapy is also an attractive treatment option, especially when rapid disease control is required. Cabazitaxel (Jevtana TM, Genzyme, Paris, France) is a microtubule inhibitor indicated in combination with prednisone for treatment of patients with metastatic CRPC previously treated with a docetaxel-containing treatment regimen. Cabazitaxel is administered intravenously every 3 weeks at a recommended dose of 25 mg/m$^2$. The TROPIC phase III clinical trial compared cabazitaxel to mitoxantrone in patients with metastatic CRPC that had previously progressed on treatment with docetaxel [16]. Seven hundred fifty-five men were randomized 1:1 to cabazitaxel 25 mg/m$^2$ IV every 3 weeks vs. mitoxantrone 12 mg/m$^2$ IV every 3 weeks. All patients received prednisone 10 mg PO daily. The median survival was significantly improved for the groups that received cabazitaxel [15.1 months (95% CI 2.4-3.0) vs. 12.7 months (11.6-13.7); p<0.0001] and so the median PFS [2.8 months (95% CI 2.4-3.0) vs. 1.4 months (95% CI 1.4-1.7); p<0.0001]. The most common clinically significant grade 4 or higher side effects of cabazitaxel were neutropenia and diarrhea. Based on those results cabazitaxel was granted approval by FDA for treatment of metastatic CRPC in that setting.

The current paradigm for treatment of castration-resistant prostate cancer is sequential exposure to drugs that have shown activity in CRPC. Several ongoing and completed clinical trials have combined the aforementioned agents in the castration-resistant setting. A phase 1/2 trial of cabazitaxel in combination with abiraterone acetate showed that the combination of full dose cabazitaxel and abiraterone acetate is well tolerated and demonstrated antitumor activity in the post-docetaxel setting [17]. Twenty-seven patients previously treated with docetaxel were enrolled. The median number of cycles with cabazitaxel was 7 (range 1-21) and the median PSA-PFS was 6.9 months (95% CI 4.1-10.2 months). Twelve patients achieved a PSA response (PSA response rate 46%; 95% CI 26.6-66.4%) and 3 out of 14 patients (21%) with measurable disease achieved a partial response per RECIST 1.1. Most common side effects were grade > 3 neutropenia (15 patients; 55%; 1 patient with febrile neutropenia), fatigue (4 patients; 15%) and sepsis (3 patients; 11%). These data support the use of combination treatment, given their acceptable safety profile and enhanced efficacy.

1.4 Rationale for correlative studies

1.4.1 Association of androgen-receptor splice variant 7 messenger RNA (AR-V7) presence in circulating tumor cells and response to treatment and outcome.

It has been shown that the detection of androgen-receptor splice variant 7 messenger RNA (AR-V7) in circulating tumor cells from patients with CRPC is associated with resistance to abiraterone acetate and enzalutamide, whereas it is not associated with resistance to taxanes [18, 19]. In an initial study, a total of 31 patients treated with enzalutamide and 31 patients treated with abiraterone acetate were prospectively evaluated for the presence of AR-V7, which was detected in 39% and 19%, respectively [18]. Among patients receiving abiraterone acetate, AR-V7 positivity was associated with lower PSA response rate (0% vs. 68%; p=0.004), and shorter PSA PFS (1.3 months vs. not reached; p<0.001), clinical or radiographic PFS (2.3 months vs. not reached; p<0.001) and OS (10.6 months vs. not reached; p=0.006). However, in patients treated with taxanes, it appears that the presence of AR-V7 does not confer resistance to treatment [19]. From the 37 taxane-treated patients, 17 (46%) were tested positive for AR-V7. Both AR-V7 positive and negative patients had similar responses to therapies, assessed both by PSA and radiographically. A pooled analysis of patients from both studies showed that outcomes were superior with taxanes compared to enzalutamide or abiraterone acetate in AR-V7-positive men (PSA responses 41% vs. 0%; p<0.001), PSA PFS (HR 0.19; 95% CI 0.07-0.52; p=0.001) and radiographic PFS (HR 0.21; 95% CI 0.007-0.59; p=0.003). Our aim is to prospectively examine a) whether patients positive for AR-V7 at baseline have a longer radiographic or clinical PFS to the combination of cabazitaxel and abiraterone acetate vs. abiraterone acetate alone; b) whether the addition of cabazitaxel can change the AR-V7 status of patients who are positive at study registration; and c) whether the addition of cabazitaxel to abiraterone acetate has any impact on future development of AR-V7 positivity at the time of disease progression.

1.4.2 Characterize the pharmacodynamic changes and response to treatment using NaF PET/CT.

The clinical course of metastatic prostate cancers is largely restricted to bone, with predominantly osteoblastic metastases. However, there is currently no validated tool to assess treatment response in patients with metastatic prostate cancer to the bone. One of the most promising PET imaging agents for detection of bone metastasis in prostate cancer is $^{18}$F-Sodium fluoride (NaF). NaF PET/CT is a more specific and sensitive tool that allows quantitative determination of change in functional disease burden to therapy. NaF PET/CT repeatability and responsiveness in patients with metastatic castration-resistant prostate cancer to bone treated with an antimicrotubule directed agent or AR-directed therapies has been previously evaluated [20]. In this study, we will prospectively examine whether the addition of cabazitaxel to abiraterone acetate can improve the overall response as well as the percentage of responding

lesions compared to abiraterone acetate alone in support of our hypothesis. NaF PET/CT scans will be analyzed with innovative image analysis technique, termed Quantitative Total Bone Imaging (QTBI), developed at the University of Wisconsin [21, 22]. NaF PET/CT image analysis will be performed at AIQ Solutions, Inc., using the FDA 510(K) cleared software.

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## 1.5 Rationale for Tobacco Use Assessment

**NOTE:** Please refer to Appendix VI for EAQ16T references.

A significant proportion of cancer patients are current smokers at the time of cancer diagnosis, [1-5] and there are known risks associated with continued smoking following cancer diagnosis. These include decreased survival time; increased complications from surgery, radiation, and chemotherapy; and increased risk of second primary tumors [6,-11] As such, the National Comprehensive Cancer Network (NCCN), the American Association of Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) have identified persistent smoking as a modifiable risk factor and recommend cessation counseling for cancer patients who smoke. Although evidence-based guidelines for treating tobacco dependence exist, [12] they have not yet been well-integrated into cancer care settings. Moreover, knowledge regarding the scope and patterns of tobacco use among cancer patients is limited.

Tobacco use following a cancer diagnosis compromises treatment outcomes but is not well understood. About 10% to 30% of cancer patients are smoking at the time of diagnosis, [1-4, 14, 1 5] and the majority of cancer patients who smoke at diagnosis continue to smoke following diagnosis [3, 16]. Quitting smoking upon cancer diagnosis may improve cancer treatment effectiveness, reduce risk of recurrence and of developing new primary tumors, [9,11,17-21] and improve chances of survival [1,22-24]. Conversely, continuing to smoke may result in diminished QOL [1, 25, 26], treatment delays and increased treatment complications [2, 6–8, 22, 27–34].

Tobacco use following a cancer diagnosis may compromise patient reported outcomes. It is hypothesized that smoking may be used as a means of reducing symptom burden among cancer patients, which may be a barrier to smoking cessation. Relatedly, research has shown that cancer patients who are smoking experience more difficulty with physical and psychological symptom control, compared to nonsmokers [35–38]. Research is needed to examine how symptom levels differ, by tobacco use and exposure and how tobacco use changes may affect reported symptom burden.

National initiatives emphasize the importance of identifying tobacco use in cancer care settings. Smoking status was designated as a core objective in the 2010 federal government “Meaningful Use” electronic health record documentation [39, 40]. In 2013, the American Association for Cancer Research (AACR) released guidelines emphasizing the provision of tobacco cessation services to cancer patients [41]. The American Society of Clinical Oncology (ASCO) recommends cessation counseling to all smokers by their second oncology visit as a core quality indicator [42]. The National Comprehensive Cancer Network (NCCN) published Smoking Cessation guidelines to formalize these initiatives [43].

Integrated, evidence-based services are needed during cancer care. The USPHS Practice Guidelines recommend that evidence-based tobacco treatment be

delivered to all smokers in health care settings, yet little progress has been made to integrate these guidelines into cancer care [44]. This is unfortunate, as cessation closer to the time of diagnosis results in a higher likelihood for continued abstinence [1,45-48] effective interventions exist, [1,45-48] and many cancer patients who smoke want to quit smoking[45,46,49,50]. Little work has been done to explore the delivery and effectiveness of tobacco treatment among racial/ethnic minority cancer patients who are at elevated risk of continued smoking [51-53].

Tobacco use is often not being assessed or intervened upon during cancer care. Recent surveys of oncologists and of clinical practices at comprehensive cancer centers and community oncology settings demonstrate that assessment of tobacco dependence is lacking [54-57]. During treatment, most cancer patients do not get assistance with smoking cessation support.58–60 Tobacco use assessments and cessation support have not been incorporated in most cooperative group clinical trials [61]. No one has assessed cancer patients' reports of their oncology providers' assistance behaviors.

The NCI-AACR Cancer Patient Tobacco Use Assessment Task Force developed the Cancer Patient Tobacco Use [1-4,13,14]. Questionnaire (C-TUQ). We propose that administering selected C-TUQ items to participants enrolling in 8 Phase II and Phase III ECOG ACRIN (EA) therapeutic trials will add value to parent trial research questions by advancing the field. Specifically, among patients with varied cancers (tobacco-related and non tobacco-related) and cancer treatments, we will administer C-TUQ questions at EA trial enrollment and 3 and 6 month follow-up.

We have the following aims:

1. Treatment toxicity: To determine the effects of tobacco, operationalized as combustible tobacco (1a), other forms of tobacco (1b), and environmental tobacco exposure (ETS) (1c) on provider-reported cancer-treatment toxicity (adverse events (both clinical and hematologic) and dose modifications).
2. Symptom burden: To determine the effects of tobacco on patient-reported physical symptoms and psychological symptoms.
3. Cessation patterns and treatment: To examine quitting behaviors and behavioral counseling/support and cessation medication utilization.
4. Trial outcomes: To explore the effect of tobacco use and exposure on treatment duration and relative dose intensity, and on therapeutic benefit, of 8 selected EA trials.

The findings will advance the nascent field of tobacco use in the context of cancer care by: 1) longitudinal assessment of cigarette smoking, other forms of tobacco use and secondhand smoke exposure at trial enrollment and at 3 and 6 month follow-up; 2) increase knowledge about the effects of tobacco use and exposure on treatment toxicity, physical and psychological symptoms and 3) oncology provider delivery, and 4) patient's perceptions of stigma and utilization of behavioral and pharmacological treatment of tobacco dependence. Finally, the use of this assessment would provide a unique additional value to the hypothesis of this trial, by allowing investigation of previously unanswered questions about the effects of tobacco use and exposure on trial adherence and outcomes among patients with smoking-related and non-smoking related cancers

## 2. Objectives

2.1 Primary Objective

2.1.1 To assess whether the addition of 6 cycles of cabazitaxel to abiraterone acetate in patients with CRPC that have previously received docetaxel and ADT for HSPC can improve PFS compared to abiraterone acetate alone.

2.2 Secondary Objectives

2.2.1 To assess whether the addition of 6 cycles of cabazitaxel to abiraterone acetate in patients with CRPC that have previously received docetaxel and ADT for HSPC can increase the percentage of change in PSA from baseline to week 12 of treatment as well as the maximum decline in PSA that occurs at any point after treatment compared to abiraterone acetate alone.

2.2.2 To assess whether the addition of 6 cycles of cabazitaxel to abiraterone acetate in patients with CRPC that have previously received docetaxel for HSPC can prolong time to PSA progression compared to abiraterone acetate alone.

2.2.3 To assess whether the addition of 6 cycles of cabazitaxel to abiraterone acetate in patients with CRPC that have previously received docetaxel for HSPC can improve radiographic response (per RECIST 1.1) compared to abiraterone acetate alone.

2.2.4 To assess whether the addition of 6 cycles of cabazitaxel to abiraterone acetate in patients with CRPC that have previously received docetaxel and ADT for HSPC can prolong the overall survival (OS) compared to abiraterone acetate alone.

2.2.5 To assess safety and tolerability of the combination of 6 cycles of cabazitaxel and abiraterone acetate.

2.3 Exploratory Objectives

2.3.1 AR-V7 Biomarker Objectives

2.3.1.1 To examine whether patients with circulating tumor cells (CTCs) positive for AR-V7 at baseline have a longer radiographic or clinical PFS to the combination of cabazitaxel and abiraterone acetate vs. abiraterone acetate alone.

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2.3.1.2 To examine whether the addition of cabazitaxel to abiraterone acetate can change the AR-V7 status of patients who are positive at study registration.

2.3.1.3 To examine whether the addition of cabazitaxel to abiraterone acetate has any impact on future development of AR-V7 positivity at the time of disease progression.

2.3.2 Imaging Objectives

2.3.2.1 To assess if the changes in total tumor burden from baseline to week 12 as assessed with NaF PET/CT will differ between two arms.

2.3.2.2 To correlate total tumor burden at the baseline as assessed with NaF PET/CT with the PFS.

2.3.2.3 To correlate heterogeneity of response from baseline to week 12 as assessed with NaF PET/CT with the PFS.

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2.3.3 Tobacco Use Objectives

2.3.3.1 To determine the effects of tobacco, operationalized as combustible tobacco (1a), other forms of tobacco (1b), and environmental tobacco exposure (ETS) (1c) on provider-reported cancer-treatment toxicity (adverse events (both clinical and hematologic) and dose modifications).

2.3.3.2 To determine the effects of tobacco on patient-reported physical symptoms and psychological symptoms.

2.3.3.3 To examine quitting behaviors and behavioral counseling/support and cessation medication utilization.

2.3.3.4 To explore the effect of tobacco use and exposure on treatment duration, relative dose intensity, and therapeutic benefit.

**NOTE:** Tobacco Use objectives described above are ancillary for the Tobacco Use Assessment project approved by NCI. A combined analysis of the data from the selected ECOG-ACRIN trials is planned. Data collected from the tobacco use assessment in each parent study will not be analyzed and reported in the clinical study report.

## 3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must 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) _____

Physician Signature and Date _____

**NOTE:** CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

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

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**NOTE:** Institutions are not required to participate in the optional NaF PET/CT sub-study.

### 3.1 Eligibility Criteria

#### 3.1.1 Inclusion Criteria

3.1.1.1 Age ≥ 18 years.

3.1.1.2 Histologically confirmed diagnosis of prostate cancer (adenocarcinoma of the prostate).

3.1.1.3 Previous chemotherapy with at least 3 cycles of docetaxel for hormone-sensitive metastatic prostate cancer.

3.1.1.4 Metastatic disease as evidenced by the presence of soft tissue and/or bone metastases on imaging studies (CT/MRI of abdomen/pelvis, bone scintigraphy or NaF PET/CT).

3.1.1.5 Ability to swallow abiraterone acetate tablets as a whole.

3.1.1.6 All patients must be receiving standard of care androgen deprivation treatment (surgical castration versus LHRH agonist or antagonist treatment); subjects receiving LHRH

agonist or antagonist must continue treatment throughout the time on this study.

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3.1.1.7 Patients must have castrate serum level of testosterone of < 50 ng/dL (< 1.73 nmol/L), confirmed ≤ 4 weeks prior to randomization.

Serum testosterone:_____ Date of test:_____

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3.1.1.8 Patients must have progressive disease while receiving androgen deprivation therapy defined by any one of the following as per the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria for PSA, measurable disease or non-measurable (bone) disease [23] during treatment with ADT:

3.1.1.8.1 PSA: At least two consecutive rises in serum PSA, obtained at a minimum of 1-week intervals, with the final value ≥ 1.0 ng/mL, confirmed ≤ 4 weeks prior to randomization

PSA:_____ Date of test:_____.

**OR**

3.1.1.8.2 Measurable disease (by RECIST 1.1): > 20% increase in the sum of the longest diameters of all measurable lesions or the development of new measurable lesions. The short axis of a target lymph node must be more that 15 mm to be assessed for change in size.

**OR**

3.1.1.8.3 Non-measurable (bone) disease: The appearance of two or more new areas of uptake on bone scan (or NaF PET/CT) consistent with metastatic disease compared to previous imaging during castration therapy. The increased uptake of pre-existing lesions on bone scan will not be taken to constitute progression, and ambiguous results must be confirmed by other imaging modalities (e.g. X-ray, CT or MRI). Clinical decisions about response or progression will be based on CT and bone scans.

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3.1.1.9 Patients may or may not have been treated previously with a nonsteroidal antiandrogen, such as flutamide, bicalutamide or nilutamide. For patients previously treated with an antiandrogen, they must be off treatment for at least 4 weeks (for flutamide) or 6 weeks (for bicalutamide or nilutamide) prior to registration and must have shown PSA progression after discontinuing the anti-androgen.

3.1.1.10 Patients must have an ECOG performance status of 0, 1, or 2.

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3.1.1.11 Adequate hematologic and renal function as evidenced by the following baseline laboratory values ≤ 4 weeks prior to randomization:

3.1.1.11.1 ANC ≥ 1500/$mm^3$

ANC:_____ Date of test:_____

3.1.1.11.2 Hgb ≥ 9.0 gr/dL

Hgb:_____ Date of test:_____

3.1.1.11.3 Platelets ≥ 100,000/$mm^3$

Platelet count:_____ Date of test:_____

3.1.1.11.4 Creatinine < 2.0 mg/dL

Creatinine:_____ Date of test:_____

3.1.1.12 Patients must be informed of the experimental nature of the study and its potential risks, and must sign an IRB-approved written informed consent form indicating such an understanding.

3.1.1.13 Patients with resected or irradiated brain metastases or those treated with stereotactic radiation therapy are eligible to enroll, provided that they do not require treatment with steroids that exceeds 10 mg of prednisone daily or equivalent.

Rev. Add#3

3.1.1.14 Sexually active males must use an accepted and effective method of double barrier contraception (vasectomy must be combined with a physical barrier method) or abstain from sexual intercourse for the duration of their participation in the study and for 26 weeks after the last dose of study drug.

3.1.2 Exclusion Criteria

Rev. Add#2

3.1.2.1 Any prior chemotherapy or AR-directed therapy for CRPC, (e.g. docetaxel, cabazitaxel, mitoxantrone, abiraterone acetate, ketoconazole, or enzalutamide). Previous treatment with radium-223, sipuleucel-T, or other immunotherapy-based treatment is allowed.

3.1.2.2 Pure small cell or other variant (non-adenocarcinoma) prostate cancer histology for which treatment with abiraterone would not be considered appropriate.

Rev. Add#2

3.1.2.3 Patients may not be receiving other therapeutic investigational agents or be receiving concurrent anticancer therapy other than standard androgen deprivation therapy. Concurrent treatment with agents to prevent skeletal-related events (such as zoledronic acid or denosumab) will be allowed as long as it was initiated prior

to study registration or there are plans to initiate it after cycle 2 day 1.

3.1.2.4 Any medical condition for which prednisone (corticosteroid) is contraindicated.

3.1.2.5 Chronic liver disease or abnormal liver function at baseline:

3.1.2.5.1 If total bilirubin is > ULN (NOTE: in subjects with Gilbert's syndrome, if total bilirubin is > ULN, measure direct and indirect bilirubin and if direct bilirubin is within normal range, subject may be eligible) or

3.1.2.5.2 Alanine (ALT) or aspartate (AST) aminotransferase > 1.5xULN.

3.1.2.6 Active infection requiring treatment with antibiotics.

3.1.2.7 History of adrenal insufficiency or hypoaldosteronism.

Rev. Add#2 3.1.2.8 Myocardial infarction or arterial thrombotic event ≤ 6 months of randomization, heart failure of New York Heart Association Class II or higher, uncontrolled angina, severe uncontrolled ventricular arrhythmia.

Rev. Add#2 3.1.2.9 External beam radiation therapy ≤ 2 weeks of registration.

3.1.2.10 Prior history of allergic reactions to G-CSF.

3.1.2.11 Prior history of allergic reactions to docetaxel and/or to medications formulated with polysorbate 80.

3.1.2.12 History of active malignancy. Patients with a history of cancer that has been adequately treated and are free of disease recurrence for 3 years or more are allowed to participate. Patients with non-melanoma skin cancers or carcinoma in situ of the bladder that have been adequately excised are eligible to participate.

3.1.2.13 Life expectancy of < 12 months at screening.

3.1.2.14 Grade ≥ 2 neuropathy.

Rev. Add#2 3.1.2.15 Uncontrolled hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg). Patients with a history of hypertension are allowed to enroll provided blood pressure is controlled with anti-hypertensive treatment.

3.2 <u>NaF PET/CT Optional Sub-Study Eligibility Criteria</u>

3.2.1 Inclusion Criteria

3.2.1.1 Ability to lie still for imaging.

3.2.1.2 Weight ≤ 300 lbs. (due to equipment specifications)

Rev. Add#2 3.2.1.3 Metastatic disease confined predominantly to the bones.

| | |
|---|---|
| Physician Signature | Date |

**OPTIONAL:** This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

Rev. Add#2 **4. CTEP Registration Procedures**

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below

| Documentation Required | IVR | NPIVR | AP | A |
|---|---|---|---|---|
| FDA Form 1572 | ✔ | ✔ | | |
| Financial Disclosure Form | ✔ | ✔ | ✔ | |
| NCI Biosketch (education, training, employment, license, and certification) | ✔ | ✔ | ✔ | |
| HSP/GCP training | ✔ | ✔ | ✔ | |
| Agent Shipment Form (if applicable) | ✔ | | | |
| CV (optional) | ✔ | ✔ | ✔ | |

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR Help Desk by email at < RCRHelpDesk@nih.gov >.

Rev. Add#3 **CTSU Registration Procedures**

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

**IRB Approval:**

Each 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 be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572

An active status on a participating roster at the registering site..

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

**Downloading Site Registration Documents:** Site registration forms may be downloaded from the EA8153 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the ECOG-ACRIN link to expand, then select trial protocol EA8153
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

**Requirements for EA8153 Site Registration:**

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted )

**Requirements for NaF PET/CT Sub-Study Participation:**

**NOTE: Institutions are not required to participate in the optional NaF PET/CT sub-study.**

- EA8153 sites that wish to participate in the NaF PET/CT sub-study will be required to meet PET/CT Scanner Qualification requirements and approval. Please refer to the NaF Site Imaging Manual for guidance on the PET/CT Scanner Qualification process.

- The NaF Site Imaging Manual is available for download on the CTSU members' website under the 'Miscellaneous' tab.

If your site is interested in NaF PET/CT sub-study participation, please contact Diana Ewen, dewen@acr.org to find out if your site is approved or what your site needs to do prior to enrolling a patient onto the sub-study

**Submitting Regulatory Documents**

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

**Required Protocol Specific Regulatory Documents**

1. 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.

2. A. CTSU IRB Certification Form.
   **Or**
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   **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

**Checking Your Site's Registration Status:**

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab

- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

**NOTE:** The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

**Patient Enrollment**

**Patients must not start protocol treatment prior to randomization.**

**Treatment must start within ten working days after randomization.**

**Patients who consent to participate in the NaF PET/CT scan sub-study must complete baseline NaF PET/CT scan prior to start of treatment.**

**NOTE: Institutions are not required to participate in the optional NaF PET/CT sub-study.**

**NOTE: Patient participation in the Tobacco Use Assessment sub-study is optional.**

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam>) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

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

4.1 Protocol Number

4.2 Investigator Identification

- Institution and affiliate name

- Investigator's name

4.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.

Rev. Add#2

4.5 Stratification Factors

- ECOG performance status of 0 vs. 1-2
- Time from initiation of ADT to the development of CRPC of ≤ 12 vs. >12 months
- Visceral metastases (non-bone, non-lymph node) status of Yes vs. No

4.6 Additional Requirements

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

**NOTE:** Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.6.2 Biological specimens are to be submitted for defined laboratory research studies and/or future undefined research per patient consent as outlined in Section 10.

Rev. Add#2

4.6.3 Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam>) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To hold the Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Rev. Add#3

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study

invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

Rev. Add#2

#### 4.6.4 Image Submission Using TRIAD

For patients who consent to participate in the NaF PET/CT scan sub-study.

TRIAD is ACR's proprietary image exchange application that will be used as the sole method of data transfer to the ACR Clinical Research Center Core Laboratory for this trial. TRIAD can be installed on one or several computers of choice within the institutional "firewall" and on the institutional network; internet access is required. The TRIAD application can then be configured as a DICOM destination on either scanner(s) and/or PACS system for direct network transfer of study related images into the TRIAD directory. When properly configured, the TRIAD software de-identifies, encrypts, and performs a lossless compression of the images before they are transferred to the ACR Imaging Core Laboratory image archive in Philadelphia.

TRIAD Access Requirements:

- Site designated staff who will submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account, and be registered as an AP, NPIVR or IVR. Please refer to CTEP Registration Procedures of the protocol for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- To submit images, the site designated image submitter should be on the site's affiliate rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role. RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:

When a user applies for a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/

This process can be done in parallel to obtaining your CTEP-IAM account username and password and RCR registration.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org or call 703-390-9858.

**NOTE** Please refrain from anonymizing the DICOM header of any exam prior to uploading into the TRIAD application. Custom DICOM editing can exclude an exam from the final analysis, due to the omission of technical data elements. These elements include, but are not limited to, the study date, scanner station name, scanner serial number, and any scan acquisition parameter. TRIAD has been uniquely configured to locate and scrub all PHI from the EA8153 DICOM headers, during the image transfer to ensure the anonymity of our trial patients

Rev. Add#2

4.6.5 ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO) System:

When patients consent to participate, they will be asked to provide a contact email address and that address along with their registration information will be sent directly from the parent trial's registration system to EASEE-PRO, and the patient will be automatically registered into EASEE-PRO for participation. To activate their account for self-directed web entry of surveys, the system will send an activation message to the contact email address that will explain how to activate their account for self-directed web entry of surveys. After their account is activated, the patient will be able to complete questionnaires using a secure browser interface from any web enabled computer, tablet, or mobile device.

Rev. Add#2

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, including disease assessment, will still be collected and must be submitted through Medidata Rave and EASEE-PRO according to the schedule in the EA8153 Forms Completion Guidelines.

## 5. Treatment Plan

### 5.1 Administration Schedule

All treatment will be administered on an outpatient basis.

Please give patients copies of the blank Patient Pill Calendars (Appendix II)

#### 5.1.1 Treatment Arm A:

5.1.1.1 Androgen deprivation therapy with either LHRH agonist or antagonist or surgical castration with bilateral orchiectomy

5.1.1.2 Abiraterone acetate 1000 mg by mouth (PO) once daily continuously, 2 hours before or after meals. Abiraterone acetate is to be taken whole tablets with water. Do not crush or chew tablets. Abiraterone acetate is to be taken on an empty stomach; however, prednisone is to be administered with food (prednisone 5 mg BID).

5.1.1.3 Prednisone 5 mg PO twice daily continuously, take with food

5.1.1.4 Cabazitaxel 25 mg/m$^2$ intravenously (IV) on day 1 every 21 days over one hour for up to 6 cycles (1 cycle = 21 days). Dose of cabazitaxel will be calculated based on actual body weight. If the patient's weight on the day of dosing differs by > 10% from the weight used to calculate the previous dose, the dose must be recalculated

5.1.1.5 G-CSF allowed per local standard practice. Examples of acceptable options include pegfilgrastim once, filgrastim or TBO-filgrastim for 5 days or equivalent

5.1.1.6 Premedication for cabazitaxel is required to decrease or prevent acute anaphylactoid reactions and to decrease the severely or delay the onset of late-occurring fluid retention problems

To be administered IV 30 minutes before each dose of cabazitaxel:

Rev. Add#3

5.1.1.6.1 Antihistamine (dexchloropheniramine 5 mg or diphenhydramine PO or IV 25 mg or equivalent antihistamine)

5.1.1.6.2 Corticosteroid (dexamethasone 8 mg or equivalent steroid)

5.1.1.6.3 H2 antagonist (ranitidine 50 mg or equivalent H2 antagonist)

5.1.1.6.4 Antiemetic prophylaxis is recommended and can be given PO or IV as needed.

#### 5.1.2 Treatment Arm B:

5.1.2.1 Androgen deprivation therapy with either LHRH agonist or antagonist or surgical castration with bilateral orchiectomy

5.1.2.2 Abiraterone acetate 1000 mg PO once daily continuously, 2 hours before or after meals. Abiraterone acetate is to be taken whole tablets with water. Do not crush or chew tablets. Abiraterone acetate is to be taken on an empty stomach; however, prednisone is to be administered with food (prednisone 5 mg BID).

5.1.2.3 Prednisone 5 mg PO twice daily continuously, take with food

Rev. Add#2

## 5.2 Adverse Event Reporting Requirements

**All toxicity grades described in this protocol and all reportable adverse events on this protocol will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.**

**All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).**

Rev. Add#2

### 5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are a required part of every clinical trial, are done so investigators and regulatory agencies can detect and analyze adverse events and risk situations to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

Rev. Add#2

### 5.2.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of an agent in humans, whether or not considered agent related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

Rev. Add4

| ATTRIBUTION | DESCRIPTION |
|---|---|
| Unrelated | The AE is *clearly NOT related* to protocol treatment. |
| Unlikely | The AE is *doubtfully related* to protocol treatment. |
| Possible | The AE *may be related* to protocol treatment. |
| Probable | The AE is *likely related* to protocol treatment. |
| Definite | The AE is *clearly related* to protocol treatment. |

- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.

- **Expectedness:** 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, when either the type of event or the severity of the event is NOT listed in the protocol or drug package insert.

Rev. Add#2

5.2.3 Mechanism for Adverse Event Reporting

**Routine reporting:** Adverse events are reported in a routine manner at scheduled times during a trial using the Medidata Rave clinical data management system. Please refer to Section 4 of the protocol for more information on how to access the Medidata Rave system and the EA8153 forms packet for instructions on what, where and when adverse events are to be reported routinely.

Rev. Add4

**Expedited reporting:** In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The remainder of this section provide information and instructions regarding expedited adverse event reporting

Rev. Add#2

5.2.4 Expedited Adverse Event Reporting Procedure

Adverse events requiring expedited reporting will use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov.

For this study, a CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov., so that ECOG-ACRIN and all appropriate regulatory agencies will be notified of the event in an expeditious manner.

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 (857-504-2900)
- 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.

5.2.5 Determination of Reporting Requirements

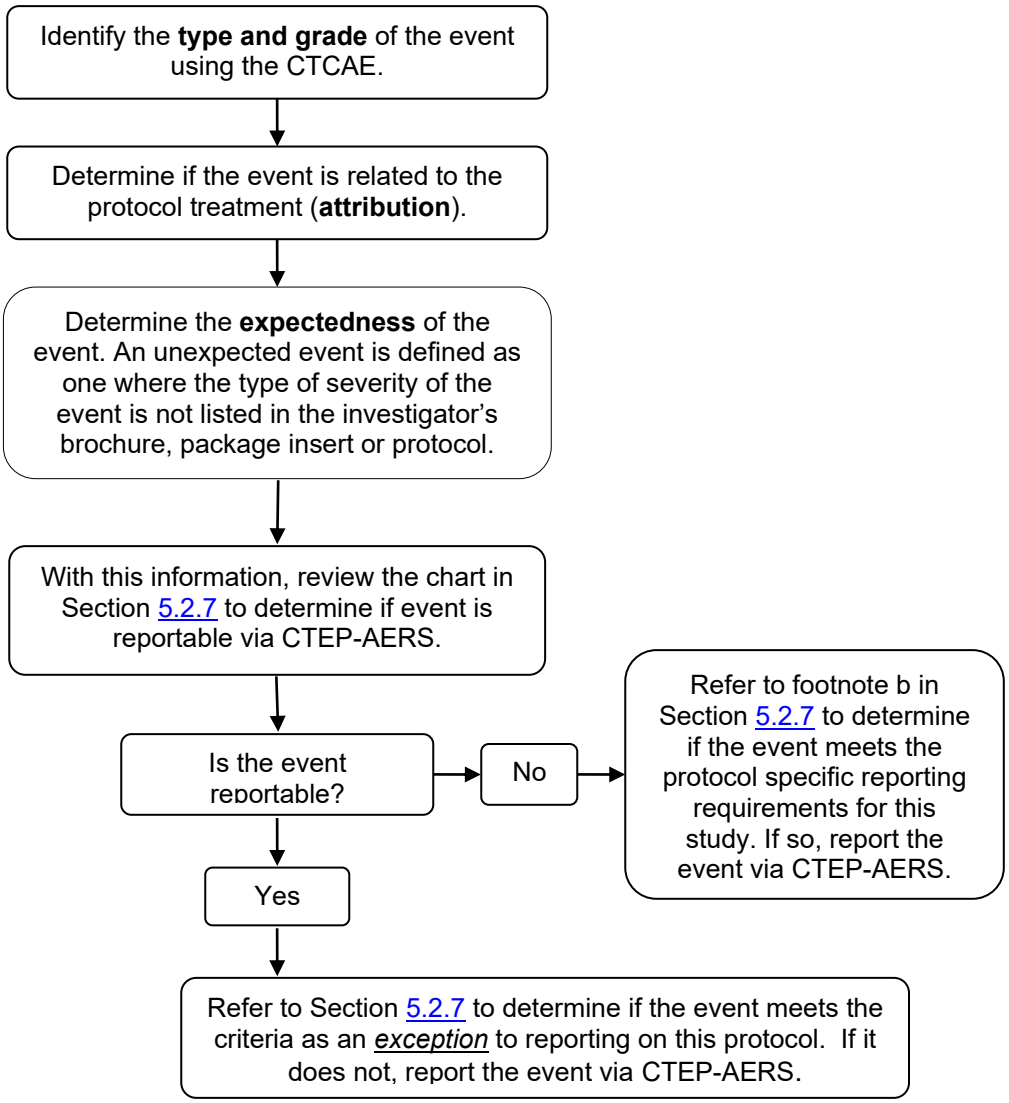
Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- the relationship to the study treatment (attribution)
- the expectedness of the adverse event

Using these factors, the instructions and tables in the following sections have been customized for protocol EA8153 and outline the specific expedited adverse event reporting requirements for study EA8153.

Rev. Add#2

### 5.2.6 Steps to determine if an event is to be reported in an expedited manner



Rev. Add#2

### 5.2.7 Expedited Reporting Requirements for Arms A and B on protocol EA8153

Commercial Agents: Abiraterone acetate, Cabazitaxel, Prednisone

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 | See footnote (b) for special requirements. |
| Unrelated or Unlikely | | | 7 calendar days | 7 calendar days | |
| 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.

Rev. Add4

**a** A death occurring while on study treatment or within 30 days of the last dose of study treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

**NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.**

**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**.

**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 *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* 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 AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

### 5.2.8 Other recipients of adverse event reports and supplemental data

Adverse events determined to be reportable via CTEP-AERS 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.

### 5.2.9 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported as follows:

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.

2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.

- **A <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**

1. Complete a Second Primary Form in Medidata Rave within 14 days.

Rev. Add4

2. Report the diagnosis on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave

   *Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy*

   **NOTE:** When reporting attribution on the AE Form, assess the relationship between the secondary malignancy and the current protocol treatment ONLY (and NOT relationship to any anti-cancer treatment received either before or after protocol treatment).

3. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov
4. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
5. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

**NOTE:** The ECOG-ACRIN 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 ECOG-ACRIN 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 ECOG-ACRIN Second Primary Form.

Rev. Add#2

## 5.3 Dose Modifications

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

Rev. Add#2

### 5.3.1 Cabazitaxel

For cabazitaxel, no more than one dose modification to 20 mg/m$^2$ should be allowed for any patient. If a patient requires a second reduction of cabazitaxel, he will continue on abiraterone acetate alone. Dose adjustment are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE). If toxicity occurs, the appropriate treatment will be used to ameliorate signs and symptoms including anti-emetics for nausea and vomiting, anti-diarrheals for diarrhea, anti-pyretics and antihistamines for drug fever before toxicity grade is determined.

Rev. Add4

Dose adjustments for toxicity should be made according to the guidelines below. Dose reduction is based on dose level. 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 abiraterone acetate alone.

| **Dose Level** | **Cabazitaxel (mg/m$^2$)** |
|---|---|
| Level 0 (starting) | 25 mg/m$^2$ |
| Level -1 | 20 mg/m$^2$ |

#### 5.3.1.1 Dose Modification 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):

| Toxicity | Dosage Modification |
|---|---|
| Prolonged grade ≥ 3 neutropenia (greater than1 week) despite appropriate medication including G-CSF | Delay treatment[a] until neutrophil count is > 1,500 cells/mm$^3$, then reduce dosage[b] of cabazitaxel to 20 mg/m$^2$. Use G-CSF for secondary prophylaxis. |
| Febrile neutropenia[c] | Delay treatment[a] until improvement or resolution, and until neutrophil count is > 1,500 cells/mm$^3$, then reduce dosage[b] of cabazitaxel to 20 mg/m$^2$. Use G-CSF for secondary prophylaxis. |
| Thrombocytopenia grade > 2 | Delay treatment[a] until platelet count > 75,000/mm$^3$, then reduce cabazitaxel dose[b] to 20 mg/m$^2$. |

[a] If planned day 1 dose must be delayed for three consecutive weeks, discontinue cabazitaxel and continue on abiraterone acetate alone.

[b] If a dose reduction is made, maintain the lower dose for all subsequent cycles.

[c] Grade > 3 neutropenia associated with fever (one reading of oral temperature > 38.5°C, or three readings of oral temperature > 38°C in a 24-hour period).

5.3.1.2 Dose Modification for Hepatic Dysfunction:

AST and total bilirubin will be evaluated at baseline and on 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:

| Total Bilirubin[a] | | AST[a] | Action |
|---|---|---|---|
| > 1 to ≤ 1.5xULN | or | ≥ 1.5xULN | Reduce dose to 20 mg/m$^2$; use with caution and monitor closely |
| > 1.5xULN | and | any | Discontinue cabazitaxel |

[a] In the absence of biliary obstruction or other contributing cause responsible for concurrent elevation.

5.3.1.3 Dose modification for Peripheral Neuropathy:

If ≥ Grade 3, the patient will discontinue cabazitaxel.

If Grade 2, cabazitaxel will be held and the patient should be retreated upon recovery to a Grade 1 toxicity with dose reduction of cabazitaxel to 20 mg/m$^2$.

If Grade 2 neurotoxicity persists for more than 3 weeks, the patient will discontinue cabazitaxel.

5.3.1.4 Dose modification for diarrhea:

Diarrhea > grade 3 or persistent despite appropriate medication, fluids, and electrolyte replacement: Delay treatment until improves or resolves and then reduce dose to 20 mg/m$^2$.

Rev. Add#2

5.3.1.5 Allergic Reactions to Cabazitaxel:

Treatment should be discontinued for Grade 4 allergic reactions. There are no dose reductions for hypersensitivity reactions.

Grade 4 allergic reactions are defined as a life-threatening event that requires pressor and/or ventilation support for shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion.

Patients with two episodes of Grade 3 Allergic reactions or one Grade 4 Allergic reaction are to discontinue cabazitaxel.

5.3.1.6 Delay of Therapy:

If cabazitaxel 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 abiraterone acetate alone.

5.3.1.7 Other Toxic Effects thought to be related to Cabazitaxel:

If clinically significant toxicities ≤ Grade 2, manage the subject symptomatically if possible, and retreat without dose reduction.

If toxicities ≥ Grade 3 and clinically significant (not mentioned above), cabazitaxel should be withheld (except for anemia as patients can be transfused) until resolution to ≤ Grade 1 or baseline if baseline was greater than Grade 1, then reinstituted, if medically appropriate, at full dose or a dose reduction of one level, as clinically indicated.

Rev. Add#2

5.3.2 Abiraterone Acetate

For abiraterone acetate, no more than two dose modifications should be allowed for any patient. If a patient requires a third reduction of abiraterone acetate, treatment with abiraterone acetate will be discontinued. Dose adjustment are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE). If toxicity occurs, the appropriate treatment will be used to ameliorate signs and symptoms including anti-emetics for nausea and vomiting, anti-diarrheals for diarrhea, anti-pyretics and antihistamines for drug fever before toxicity grade is determined.

Rev. Add4

Dose adjustments for toxicity should be made according to the guidelines that follow. Dose reduction is based on dose level. If a dose is reduced due to toxicity the dose will not be re-escalated to starting level. Exceptions apply if dose reduction to abiraterone acetate happened during concurrent treatment with cabazitaxel and after treatment with cabazitaxel is completed or discontinued. In those cases, re-escalation of abiraterone acetate should be discussed and approved by the study chair. Treatment [abiraterone] may be delayed no more than eight weeks to allow recovery from drug-related toxicity.

Rev. Add#3

If treatment must be delayed longer than eight weeks from scheduled day of dosing, patient will be taken off study.

| Dose Level | Abiraterone Acetate |
|---|---|
| Level 0 (starting) | 1000 mg once daily |
| Level -1 | 750 mg once daily |
| Level -2 | 500 mg once daily |

5.3.2.1 Dose modification for Hepatic Dysfunction:

AST and total bilirubin will be evaluated at baseline and every 21 days for the first 18 weeks and every 6 weeks thereafter.

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

| Total Bilirubin[a] | | AST[a] | Action |
|---|---|---|---|
| > 3xULN | or | >5xULN | Withhold treatment until return to baseline or AST ≤ 2.5xULN and total bilirubin ≤ 1.5xULN, then reinitiate at 750 mg once daily. |
| Recurrence as above at lower dose of 750 mg once daily | | | Withhold treatment until return to baseline or AST ≤ 2.5xULN and total bilirubin ≤ 1.5xULN, then reinitiate at 500 mg once daily. |
| Recurrence as above at lower dose of 500 mg once daily | | | Discontinue abiraterone acetate |
| > 2xULN | and | > 3xULN | Discontinue abiraterone acetate |
| [a] In the absence of biliary obstruction or other contributing cause responsible for concurrent elevation. | | | |
| For patients been retreated, AST and total bilirubin should be monitored at a minimum of every 2 weeks for the first 3 months and monthly thereafter. | | | |

Rev. Add#2

5.3.2.2 Dose Modification for Hypokalemia:

At the initial observation of hypokalemia (serum potassium < 3.5 mmol/L or below lower limit of normal range, but ≥ 3.0 mmol/L), oral potassium supplement should be initiated, as per table below. The dose of potassium supplement must be carefully titrated to maintain serum potassium from 3.5 to 5.0 mmol/L. Any subject with low potassium during the study or a history of hypokalemia from a preexisting or concurrent medical condition should undergo at least weekly laboratory electrolyte evaluation. The investigator should consider maintaining potassium ≥ 4.0 mmol/L in these subjects.

If any subject experiences Grade 3 hypokalemia (serum potassium levels < 3.0 to 2.5 mmol/L) or life-threatening hypokalemia with potassium levels < 2.5 mmol/L (National

Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] hypokalemia Grade 4), abiraterone acetate treatment should be withheld and it is recommended that the subject be hospitalized for IV potassium replacement and cardiac monitoring. Re-initiation of abiraterone acetate treatment after normalization of potassium levels must be discussed with and approved by the study chair.

| Serum Potassium | Grade of Hypokalemia | Action | Further Action of Maintenance |
|---|---|---|---|
| Low potassium or history of hypokalemia | | At least weekly laboratory electrolyte evaluation | Titrate dose to serum potassium >3.5 to <5.0 mmol/L; maintenance at > 4.0 mmol/L is recommended |
| < LLN – 3.0mmol/L | Grade 1 or 2 | Initiate oral potassium supplementation | Titrate dose to serum potassium >3.5 to <5.0 mmol/L; maintenance at > 4.0 mmol/L is recommended |
| < 3.0 to 2.5 mmol/L | Grade 3 | Withhold abiraterone acetate and initiate IV potassium supplementation and cardiac monitoring | Call study chair before re-initiating abiraterone acetate |
| < 2.5 mmol/L | Grade 4 | Withhold abiraterone acetate and initiate IV potassium supplementation and cardiac monitoring | Call study chair before re-initiating abiraterone acetate |

Rev. Add#2

5.3.2.3 Dose Modification for Hypertension and Edema/Fluid Retention:

For patients that develop hypertension and/or edema/fluid retention while on treatment with abiraterone acetate, dose adjustment should be done as follows:

| Hypertension | Action | Dose of Abiraterone Acetate |
|---|---|---|
| Grade 1 to 2 | Continue 1000 mg daily | No change in the dose |
| Grade ≥ 3 | Withhold abiraterone acetate and adjust/add medication to mitigate toxicity | When grade decreases to grade ≤ 1 or baseline, resume abiraterone acetate at the full dose |
| First recurrence grade ≥ 3 | Withhold abiraterone acetate and adjust/add medication to mitigate | When grade decreases to grade ≤ 1 or baseline, resume abiraterone acetate at 750 mg daily |

| | | |
|---|---|---|
| | toxicity | |
| Second recurrence grade > 3 | Withhold abiraterone acetate and adjust/add medication to mitigate toxicity | When grade decreases to grade ≤ 1 or baseline, resume abiraterone acetate at 500 mg daily |
| Third recurrence grade ≥ 3 | Discontinue | Discontinue |

5.3.2.4 Delay of Therapy:

If abiraterone acetate has to be delayed for more than 8 weeks from planned day of dosing because of any treatment-related toxicity, then the patient will be taken off study.

5.3.2.5 Other Toxic Effects Thought to be related to Abiraterone Acetate:

If toxicities ≤ Grade 2, manage the subject symptomatically if possible, and retreat without dose reduction.

Rev. Add#3

If toxicities ≥ Grade 3 and clinically significant (not mentioned above), abiraterone acetate should be withheld until resolution to ≤ Grade 1 or baseline if baseline was greater than Grade 1, then reinstituted, if medically appropriate, at a dose reduction of one level. No dose reduction below 500 mg daily will be allowed.

5.3.3 Prednisone

Dose of prednisone may be reduced to 5 mg PO daily if clinically indicated at the discretion of the treating physician.

5.4 Supportive Care

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

5.4.2 Growth factor support per local standard practice (pegfilgrastim, filgrastim, TBO-filgrastim, lenograstim or equivalent)

5.4.3 Caution advised when study drugs are co-administered with other drugs, over-the-counter or herbal medicines that are CYP450 isoenzymes.

5.4.4 Use of agents to prevent skeletal-related events (such as zoledronic acid or denosumab) will be allowed if initiated prior to registration or after Day 1 of Cycle 2.

Rev. Add#2

5.5 Patient Reported Outcome Measures: Tobacco Use Assessment (Optional)

Assessments will be captured directly from the participants using the EASEE-PRO portal. When patients consent to participate, they will be asked to provide a contact email address and that address along with their registration information will be sent directly from the parent trial's registration system to EASEE-PRO, and the patient will be automatically registered into EASEE-PRO for participation. To activate their account for self-directed web entry of surveys, the system will send an activation message to the contact email address that will explain how to

activate their account for self-directed web entry of surveys. After their account is activated, the patient will be able to complete questionnaires using a secure browser interface from any web enabled computer, tablet, or mobile device.

The Core and Extension C-TUQ items will be assessed, together with patient-reported physical and psychological symptoms (See Table 2). Specifically, these items will be administered using the EASEE-PRO system described in the companion EA NCORP application. The advantage of our virtual electronic data capture system is that our proposed assessments will not be limited to, or dependent upon, patient trial visits. Confidential and potentially stigmatizing information can be provided without requiring direct contact with the care team.

The selected Core and Extension C-TUQ items (from categories of Basic Tobacco Use Information, Tobacco Use in Relation to Cancer Diagnosis and Treatment, Smoking Cessation/Cessation Products/Assistance Methods, Use of Other Products, and Second-Hand Smoke Exposure) will be assessed. The 4-item Short Form PROMIS® for anxiety and depression, the Lung Cancer Stigma Scale, and six symptom items (general pain, fatigue, nausea, cough, sleep difficulties, shortness of breath) from FACIT (Functional Assessment of Chronic Illness Therapy) together with modifications of these same six questions to address the degree of bother associated with each symptom will be administered as well. Additionally, we will ask participants' perceptions of how smoking improves or worsens each of the six symptom experience. All these items will be compiled into Survey of Tobacco Use (STU). Detailed information on various measures is outlined in Appendix VI.

Contents and Corresponding Questions in Survey of Tobacco Use (STU)

| Dimension | Source of Measures | Baseline STU | Follow-up STU |
|---|---|---|---|
| Basic Tobacco Use Information | C-TUQ | Q1 – Q5 | Q1 – Q2 |
| Tobacco Use in Relation to Cancer Diagnosis and Treatment | C-TUQ | Q6 – Q7 | Q3 |
| Smoking Cessation, Cessation Products, and Assistance Methods | C-TUQ | Q8 – Q13 | Q4 – Q9 |
| Use of Other Products | C-TUQ | Q14 | Q10 |
| Second-Hand Smoke Exposure | C-TUQ | Q15 – Q16 | Q11 – Q12 |
| Psychological Symptoms | PROMIS<br>Lung Cancer Stigma Scale | Q17 – Q18 | Q13 – Q14 |
| Physical Symptoms | FACIT | Q19 | Q15 |
| Sociodemographics | | Q20 – 21 | |

**NOTE**: In order to minimize ambiguity and assure that patients are oriented to answer appropriately, the specific phrasing of items may vary depending specific cancer type and treatment.

5.5.1 Assessment Schedule

Survey of Tobacco Use will be administered at the following time points:

1. at baseline (trial enrollment)
2. at 3 month follow-up from study registration
3. at 6 month follow-up from study registration

## 5.6 Duration of Therapy

Patients will receive protocol therapy unless:

- 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 EA8153 Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Radiographic or symptomatic progression as defined by Section 6 of the protocol.
- The treating physician determines they are no longer benefiting from protocol therapy.

## 5.7 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 5 years from the date of registration and data may be collected by telephone interview or chart review.

# 6. Measurement of Effect

## 6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 9 weeks for the first 18 weeks and every 12 weeks thereafter.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [24]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in RECIST.

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.
2. Measurable disease is defined by the presence of at least one measurable lesion.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

### 6.1.1 Definitions

Evaluable for Objective Response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

**NOTE:** Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.

Evaluable Non-Target Disease Response

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target lesion assessment. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

### 6.1.2 Disease Parameters

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT or MRI scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

**NOTE:** Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT or MRI scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Non-measurable also includes lesions that are < 20 mm by chest x-ray.

**NOTE:** Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of unequivocal progression of each should be noted throughout follow-up.

6.1.3 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.

6.1.4 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before registration.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest X-ray

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

Conventional CT and MRI

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of

disease. Furthermore, as with CT, the modality used at follow-up must be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

FDG-PET

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of

disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

**NOTE:** A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.1.5 Methods for Evaluation of Bone Disease

Bone disease will be evaluated using radionuclide bone scan.

Rev. Add#2

6.1.6 Evaluation of Radionuclide Bone Scans

Interpretation of serial changes in a radionuclide bone scan is well recognized to be highly subjective. Thus, the primary outcome will be whether the bone scan is stable or improved, vs. worse or progression. Changes in intensity will not be used as an outcome measure. The 2+2 rule will be applied for interpretation of bone scans:

**Stable or Improved**: Include 1) resolution of skeletal lesions, 2) absence of new skeletal lesions or 3) the appearance of new skeletal lesions on the first post-treatment scan with absence of at least 2 additional skeletal lesions in the next (confirmatory) scan performed 6 or more weeks later. Changes in intensity of a preexisting lesion will be considered stable disease unless associated with other signs of progression.

Rev. Add4

Progression (Non-Response): For patients with 2 or more new lesions in the first post-treatment scan, the appearance of at least 2 additional new lesions on a subsequent scan must be documented to qualify for disease progression. For patients with no new lesions in the first post-treatment scan, the appearance of at least 2 or more new lesions must be documented to qualify for disease progression. In all cases, these lesions must be confirmed by a subsequent (confirmatory) scan. The day of progression is the day that the first 2 lesions following the first post-treatment scan were noted. An increase in the size or intensity of known skeletal lesions will not be considered progression.

6.1.7 Response Criteria

Rev. Add#2

6.1.7.1 Evaluation of Target Lesions

<u>Complete Response (CR)</u>

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

**NOTE:** The appearance of one or more new lesions is also considered progression, See Section 6.1.7.3.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study registration at a minimum interval of 12 weeks.

Rev. Add#2

6.1.7.2 Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD

Persistence of one or more non-target 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 registration at a minimum interval of at least 12 weeks.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (see Section 6.1.7.3). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in

target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from "trace" to "large", an increase in nodal disease from "localized" to "widespread", or an increase sufficient to require a change in therapy.

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

6.1.7.3 Evaluation of New Lesions

Rev. Add#2

The appearance of new lesions constitutes Progressive Disease (PD). For bone lesions please refer to Section 6.1.6.

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if it:

a) increases in size to ≥ 15 mm in the short axis, or

b) there is new pathological confirmation that it is disease (regardless of size).

c) new effusion or ascites that appears during treatment should only be reported as a new lesion (and therefore progressive disease) if it has cytological confirmation of malignancy.

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6.1.7.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or non-protocol therapy, 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 non-target 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 registration at a minimum interval of at least 8 weeks.

**Overall Response for all Possible Combinations of Tumor Response**

**NOTE:** For this protocol, time to radiographic progression is being evaluated and the following table will apply.

| Target Lesions | Non-Target Lesions | New Lesions* | Bone Lesions | Best Overall Response | Remarks |
|---|---|---|---|---|---|
| CR | CR | No | Stable or Improved | CR | |
| CR | Non-CR/Non-PD*** | No | Stable or Improved | PR | |
| CR | Not evaluated | No | Stable or Improved | PR | |
| PR | Non-PD***/not evaluated | No | Stable or Improved | PR | |
| SD | Non-PD***/not evaluated | No | Stable or Improved | SD | Documented at least once ≥ 12 wks. from study registration |
| PD | Any | Yes or No | Any | PD | No prior SD, PR or CR |
| Any | PD** | Yes or No | Any | PD*** | |
| Any | Any | Yes | Any | PD | |
| Any | Any | Yes or No | PD | PD | |

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.

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

## 6.2 Serological Response

### 6.2.1 Response according to PSA levels

PSA levels will be assessed at the time of randomization, then every 3 weeks for the first 18 weeks and then every 6 weeks thereafter. Patient's PSA will be assigned a response according to the following criteria:

**Complete Serological Response (CR):** PSA level less than 0.02 ng/mL measured for 2 consecutive measurements at least 3 weeks apart.

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**Serological Partial Response (PR):** Decline of PSA value, referenced to the PSA at time of study entry level, by greater than or equal to 50% for 2 consecutive measurements at least 3 weeks apart.

**Serological Progression (PD):** Increase in PSA to more than 25% of nadir and ≥ 2 ng/mL above the nadir, taking as reference the lowest recorded PSA since starting treatment on the study. Two consecutive increases must be documented with each measurement obtained at least 3 weeks apart (i.e., a confirmed rising trend). On occasions, there may be an intermediate fluctuant value. This will not restart the evaluation period so long as the intermediate value was not below the previous nadir. The date of the first recorded increase that meets the criteria above (not defeated by a subsequent drop in PSA level to create a new nadir) will be deemed the date of progression. Early rises in PSA (before 12 weeks from initiation of therapy) will be ignored in determining disease progression.

## 6.3 Endpoint Definitions

### 6.3.1 Progression-Free Survival (PFS)

PFS is defined as time from randomization to radiographic progression, symptomatic deterioration or death, whichever occurs first. Patients who are alive without documented progression or symptomatic deterioration will be censored at the date of last disease assessment.

### 6.3.2 Time to PSA progression

Time to PSA progression is defined as time from randomization to PSA progression as defined in 6.2.1.

### 6.3.3 Radiographic response

Radiographic response, either CR or PR, is defined by RECIST 1.1 as per Section 6.1.

### 6.3.4 Overall survival (OS)

OS is defined as time from randomization to death or date last known alive.

## 7. Study Parameters

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### 7.1 Therapeutic Parameters

1. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done ≤ 4 weeks prior to randomization.
2. Prestudy laboratories outlined in Sections 3 and 7.1 must be done and resulted ≤ 4 weeks prior to randomization.

| | Baseline | Daily (on treatment) | Day 1, Cycle 1[a] | Day 1, Cycle 2-6[a] | Follow-up: Every 6 weeks (+/- 3 days)[b] | End of treatment[c] | Long-Term Follow-up[d] |
|---|---|---|---|---|---|---|---|
| Rev. Add#3 Abiraterone acetate (Daily, Both Arms) | | X | X | X | X | | |
| Prednisone (Daily, Both Arms) | | X | X | X | X | | |
| Cabazitaxel (Arm A only) | | | X | X | | | |
| Demographics, Medical History, Height | X | | | | | | |
| Concurrent meds | X | | X | X | X | | |
| Physical exam, interval history, vital signs, weight, ECOG performance status, survival status. | X | | X | X | X | X | |
| CBC with differential, platelets | X | | X[j] | X[j] | X[j] | X | |
| Serum chemistry[e] | X | | X[j] | X[j] | X[j] | X | |
| PSA | X | | X[j] | X[j] | X[j] | X | X[d] |
| Rev. Add4 EKG (as clinically indicated) | X | | | | | | |
| Adverse event evaluation | | | X | X | X | X | X[d] |
| Tumor measurements (CT scan of the chest/abdomen/pelvis and bone scan) | X | | Radiologic tumor measurements on treatment are to be performed every 9 weeks (+/- 7 days) for the first 18 weeks and every 12 weeks (+/- 7 days) thereafter from the patient's treatment start date. Documentation (radiologic) must be provided for patients removed from study for progressive disease | | | X[c] | X[d] |
| (OPTIONAL) NaF PET/CT[f] | X[g] | | | X[h] | | | |
| (OPTIONAL) Tobacco Use Assessment PROs[i] | See Section 5.6 | | | | | | |

a. One cycles equals 21 days (+/- 3 days)

Rev. Add#3 b. Starting 21 days (+/-3 days) from the last dose of cabazitaxel (21 days +/- 3 days after cycle 6 day 1)

Rev. Add4 c. Off-study evaluation ≤ 30 days after last treatment on study and prior to starting new therapy. Scans do not need to be repeated at the end of the study visit if progression was noted.

d. **The following will be required during Long Term Follow Up**

- **Patients that discontinue protocol treatment due to radiographic progression:** Survival status updates only*
- **Patients that discontinue protocol treatment due to symptomatic deterioration:** CT chest/abdomen/pelvis, bone scan**, & survival status updates*
- **Patients that discontinue protocol treatment before radiographic progression or symptomatic deterioration, but have serologically progressed:** CT chest/abdomen/pelvis, bone scan**, & survival status updates*

**NOTE:** Patients that have serologically progressed are not required to discontinue protocol treatment.

**Patients that discontinue protocol treatment for reasons other than serological progression, radiographic progression, or symptomatic deterioration:** PSA, CT chest/abdomen/pelvis, bone scan**, & survival status updates*

*Survival data will be collected for all patients either by phone or during office visit every 3 month is patient is < 2 years from study entry, every 6 months if patient is 2-3 years from study entry and then annually for up to year 5.

**Patients that require scans in follow-up: every effort should be made to have a radiographic assessment with CT scan and bone scan done every 3 months until radiographic or clinical progression. Patients do not have to repeat scans after they have disease progression.

**NOTE:** Please refer to Section 6 for definitions of progression

**NOTE:** Serious Adverse Events (SAEs) that meet the requirements in Section 5.2 should continue to be reported via CTEP-AERS for all patients in long-term follow up, even if they have progressed

e. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Testosterone due at baseline only.

f. Please see Section 4.6.4 for image submission instructions to submit NaF PET/CT scan images for patients consented to the NaF PET sub-study.

g. Within 7 days prior to starting treatment.

h. Day 85 +/- 7 days.

i. Tobacco use assessment PROs will be collected using EASEE-PRO for consenting patients.

j. Can be obtained within 72 hours prior to visit.

## 7.2 Biological Sample Submissions

Specimens are to be submitted as outlined in Section 1.

All specimens must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS).

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| Biological Materials[1] | Prior to Start of Treatment | Day 85 | Time of Disease Progression | Submit to: |
|---|---|---|---|---|
| From patients who answer "Yes" to "I agree to have my samples collected and I agree that my samples and related information may be used for the laboratory studies." | | | | |
| Peripheral Blood (two 8.5mL ACD yellow top tubes) | X[2] | X[3] | X[4] | Johns Hopkins University |
| From patients who answer "Yes" to "I agree to provide additional blood for research." | | | | |
| Peripheral Blood (two 10mL Streck Cell-Free DNA tubes) | X[2] | X[3] | X[4] | CBPF |

1. Kits are being provided for the collection and shipment of the blood specimens. See Appendix IV for instructions. Kit orders will on average be delivered within three (3) business days from the time the order is placed.
2. Within seven (7) days prior to starting treatment.
3. +/- seven (7) days.
4. Within 30 days from last treatment on study and prior to starting new therapy

## 8. Drug Formulation and Procurement

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Abiraterone acetate and prednisone are commercially available and guideline endorsed treatment options for patients with prostate cancer. Drug will be obtained from commercial supply.

Genzyme is supplying **Cabazitaxel** free of charge and will be distributed by Patwell Pharmaceutical Solutions. Under no circumstances can commercially supplied **cabazitaxel** be used or substituted for the patient specific **cabazitaxel** supplied by Genzyme.

8.1 Abiraterone acetate

8.1.1 Other Names

Zytiga

8.1.2 Classification

Androgen biosynthesis inhibitor

8.1.3 Mode of Action

Selectively and irreversibly inhibits CYP17(17 alpha-hydroxylase/C17,20-lyase ), an enzyme required for androgen biosynthesis which is expressed in testicular, adrenal, and prostatic tumor tissues. Inhibits the formation of testosterone precursors dehydroepiandrosterone (DHEA) and androstenendione.

8.1.4 Storage and Stability

Store at room temperature Store at room temperature (20° to 25°C [68° to 77°F]), with excursions permitted between 15° and 30°C (59° and 86°F).

8.1.5 Dose Specifics

Starting dose: 1000mg PO daily - continuously

8.1.6 Preparation

N/A

8.1.7 Route of Administration

Oral.

8.1.8 Incompatibilities

N/A

8.1.9 Availability

Commercial.

8.1.10 Side Effects

≥ 10% of patients may experience fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

Most common Labs abnormalities >20% include anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia,

hypercholesteremia, hyperglycemia, elevated AST/ALT, hypophosphatemia, and hypokalemia.

8.1.11 Nursing/Patient Implications

Hazardous agent. Use appropriate precautions for handling, administration and disposal.

8.1.12 References

Lexicomp

8.2 Cabaxitaxel

Please refer to the package insert or institutional preparation guidelines for additional information.

8.2.1 Other Names

Jevtana

8.2.2 Classification

Taxoids, antineoplastic agent

8.2.3 Mode of Action

Cabazitaxel is a taxane derivative that is microtubule inhibitor; it binds to tubulin promoting assembly into microtubules and inhibiting disassembly which stabilizes microtubules, This inhibits microtubule depolymerization and cell division, arresting the cell cycle and inhibiting tumor proliferation. Unlike other taxanes, cabazitxel has a poor affinity for MDR proteins, therefore conferring activity in resistant tumors.

8.2.4 Storage and Stability

Store at room temperature Store intact vials at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). Do not refrigerate.

8.2.5 Dose Specifics

Starting dose: 25 mg/m2

8.2.6 Preparation

Do not prepare or administer in PVC containing infusion containers or polyurethane infusion sets. Both Cabazitaxel and diluent vials contain overfill.

- Slowly inject the entire contents of the provided diluent vial into the cabazitaxel 60mg/1.5ml via, directing the diluent down the vial wall. Mix gently by inverting the vial for at least 45 seconds. Do NOT shake. Allow vial to sit so that foan dissipates and solution appears homogeneous. This results in a concentration of 10mg/ml. Use within 30 mins of reconstituting vial.
- Withdraw calculated dose and add to a 250ml D5W or NS non PVC infusion container for a final concentration of 0.1 to 0.26mg/ml. (total doses >65mg will require larger infusion volumes). Gently invert container to mix. Do not use if

crystals/precipitate appear. Infusion should be completed within 8 hours if stored at room temperature. For infusion solution stored under refrigeration, the infusion should be completed within 24 hrs.

8.2.7 Route of Administration

Intravenous.

8.2.8 Incompatibilities

N/A

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8.2.9 Availability

Cabazitaxel is provided free of charge by Genzyme and will be distributed by Patwell Pharmaceutical Solutions. Cabazitaxel is supplied in a single-use 60mg/1.5mL vial.

**Cabazitaxel should only be ordered for patients randomized to Arm A.**

**Initial Drug Orders for Each Patient**

Following randomization to Arm A, a supply of Cabazitazel may be ordered. Investigators must email a completed EA8153 Cabazitaxel Study Drug Request Form to the ECOG-ACRIN Drug Team at 900.drugorder@jimmy.harvard.edu or send by fax to (617) 589-0919. A copy of the EA8153 Cabazitaxel Study Drug Request Form is available for download from the CTSU website (www.ctsu.org). **No starter supplies are available for this protocol.**

Please refer to Appendix V for the EA8153 Cabazitaxel Study Drug Request Form download instructions.

Cabazitaxel will be shipped to a responsible person (e.g., a pharmacist) at the investigator's institution. **Sites should order enough vials to complete 3 cycles of treatment (1 vial/cycle = 3 vials needed).**

**Institutions should allow up to 4 business days to receive drug onsite. Patwell Pharmaceutical Solutions will ship and arrange drug deliveries to sites on business days only; there will be no weekend or holiday delivery of drugs.**

**IMPORTANT REORDER INSTRUCTIONS**

Once it is determined that the patient will continue treatment, please reorder **3 cycles of treatment (1 vial/cycle = 3 vials needed)** of study drug immediately byemailing a completed EA8153 Cabazitaxel Study Drug Request Form to the ECOG-ACRIN Drug Team at 900.drugorder@jimmy.harvard.edu or send by fax to (617) 589-0919 Institutions should keep in mind the number of vials used per cycle, and that Cabazitaxel is provided in in single-use 60mg/1.5mL vials.

Institutions should allow up to 4 business days to receive drug onsite. Patwell Pharmaceutical Solutions will ship and arrange drug deliveries to sites on business days only; there will be no weekend or holiday delivery of drugs.

**Drug Destruction and Return**

At the completion of each patient's treatment at your institution, all unused drugs, partially used, or empty containers must be destroyed at the site according to the institution's policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities.

Please refer to Appendix V for 'EA8153 Investigational Product Destruction Record' download instructions.

**Drug Inventory Records**

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The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.2.10 Side Effects

≥ 10% (all grades) of patients experienced neutropenia, anemia, leukopenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia.

Warning: severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasms. All patients should receive premedication.

8.2.11 Nursing/Patient Implications

Hazardous agent. Use appropriate precautions for handling, administration and disposal. Infuse over 1 hour using a 0.22 micron in- line filter. Allow infusion bag to reach room temperature prior to infusing. Premedicate with an antihistamine, a corticosteroid, and an H2 antagonist at least 30 minutes prior to infusion.

8.2.12 References

Lexicomp

8.3 Prednisone

8.3.1 Other Names

Deltasone, Orasone, Medicorten, Panasol-S, Liquid-Pred, others.

8.3.2 Classification

Adrenal corticosteroid

8.3.3 Mode of Action

Prednisone is a potent synthetic glucocorticoid that affects almost every body system. It has anti-inflammatory, immunosuppressant, and minimal mineralocorticoid activity, and antineoplastic properties. As an antineoplastic agent, prednisone may bind to specific proteins

(receptors) within the cell forming a steroid-receptor complex. Binding of the receptor-steroid complex with nuclear chromatin alters mRNA and protein synthesis within the cell.

8.3.4 Storage and Stability

The drug is stored at room temperature in a dry place.

8.3.5 Dose Specifics

Starting dose: 5mg PO BID - continuously

8.3.6 Preparation

N/A

8.3.7 Route of Administration

Oral.

8.3.8 Incompatibilities

N/A

8.3.9 Availability

Commercial.

8.3.10 Side Effects

1. Gastrointestinal: Nausea, vomiting, anorexia; increased appetite and weight gain; peptic ulceration.
2. Dermatologic: Rash; skin atrophy; facial hair growth, acne, facial erythema; ecchymoses.
3. Genitourinary: Menstrual changes (amenorrhea, menstrual irregularities).
4. Neurologic: Insomnia; muscle weakness; euphoria, psychosis, depression; headache, vertigo, seizures.
5. Cardiovascular: Fluid retention and edema; hypertension.
6. Ocular: Cataracts; increased intraocular pressure; exophthalmos.
7. Metabolic: Hyperglycemia; decreased glucose tolerance; aggravation or precipitation of diabetes mellitus; adrenal suppression; Cushingoid features; hypokalemia.
8. Hematologic: Leukocytosis.
9. Other: Osteoporosis (and resulting back pain); serious infections including herpes zoster, varicella zoster, fungal infections, pneumocystis carinii, tuberculosis; muscle wasting; delayed wound healing; suppression of reactions to skin tests.

8.3.11 Nursing/Patient Implications

1. Instruct patients to take prednisone after meals. Should not be taken too close to bedtime to avoid insomnia. A mild sedative may be required.
2. GI symptoms should be treated symptomatically.
3. Monitor blood glucose levels.
4. Educate patient concerning potential mood swings.

5. Gradual tapering of doses after long-term use should be employed.

8.3.12 References

Lexicomp

Pickup ME: Clinical pharmacokinetics of prednisone and prednisolone. Clin Pharmacokinet 4:111-128, 1979.

The Boston Collaborative Drug Surveillance Program: Acute reactions to prednisone in relation to dosage. J Clin Pharmacol 13:694-698, 1972.

Ling MHM, Perry PJ, Tsuang MT: Side effects of corticosteroid therapy: Psychiatric aspects. Arch Gen Psychiatry 38:471-477, 1981.

# 9. Statistical Considerations

## 9.1 Primary Objective

The primary objective of this randomized phase II study is to determine whether the addition of 6 cycles of cabazitaxel to abiraterone acetate (Arm A) improved progression-free survival (PFS) compared to abiraterone acetate alone (Arm B) in patients with castration-resistant prostate cancer (CRPC) that have previously received docetaxel and androgen deprivation therapy (ADT) for hormone-sensitive prostate cancer (HSPC). PFS is defined as time from randomization to radiographic progression, symptomatic deterioration or death, whichever occurs first. Patients who are alive without documented progression or symptomatic deterioration will be censored at the date of last disease assessment.

Prior studies have shown a median PFS of 5.6 months among metastatic CRPC patients treated with abiaterone acetate after receiving docetaxel for CRPC and a median PFS of 16.5 months among chemotherapy-naïve patients treated with abiraterone acetate for metastatic CRPC. Therefore, we assume a median PFS of 12 months among the study population who are treated with abiraterone acetate alone and consider a 50% improvement, to a median PFS of 18 months, to be of interest for the combination arm.

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## 9.2 Study Design

CRPC patients who have previously received docetaxel and ADT for HSPC will be randomized with a 1:1 randomization scheme to arms A and B. Stratification factors include ECOG performance status (0 vs. 1-2), time from initiation of ADT to the development of CRPC (≤ 12 months vs. > 12 months) and presence of visceral metastases (Yes vs. No).

We aim to accrue 105 patients per arm for a total of 210 patients in this study. E3805 accrued 16 patients per month in the last two years of accrual. Currently docetaxel is given to metastatic prostate cancer patients with high-volume disease, and about 65% of patients on E3805 had high-volume disease. As the proposed study is a phase II trial, we expect to accrue 6 patients per month. The total accrual will be completed in about 35 months. All patients will be followed for an additional 18.5 months. With the proposed design, the study has 90% power to distinguish an 18-month median PFS in the combination arm from a 12-month median PFS in the abiaterone alone arm using a one-sided stratified logrank test with 10% type I error. Full information will exist when 166 of the 210 patients in the two arms have progressed or died. The primary comparison will be an intention to treat analysis of all randomized patients. Although patients will be stratified by ECOG performance status, time to CRPC development and presence of visceral metastases, no subgroup analyses based on these characteristics are planned.

There will be two interim analyses conducted at 33% (55 PFS events; projected to occur at 22.5 months after study activation) and 67% (111 PFS events; projected to occur after the end of the accrual period at 35 months) information. The overall type I error will be controlled using an O'Brien-Fleming boundary function. Repeated confidence interval will be used for futility monitoring. If the repeated two-sided 80% confidence interval on the hazard ratio does not contain the target alternative hazard ratio (arm A vs. arm B) of 0.67, the Data Safety Monitoring Committee may consider stopping the trial early. If the interim logrank

test is positive, the study can be reported early before the projected end of the follow-up period. Under the accrual and failure rate assumptions above, the following table gives the operating characteristics for PFS interim and final analyses. 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 Analysis | Real Time (Months) | Information Time | Number of Failures under Alternative Hypothesis | Nominal Significance | Upper Boundary | Lower Boundary for Futility Monitoring | Number of Patients |
|---|---|---|---|---|---|---|---|
| 1 | 22.5 | 0.33 | 55 | 0.0043 | 2.6269 | -1.1162 | 135 |
| 2 | 35 | 0.67 | 111 | 0.0430 | 1.7171 | 0.4055 | 210 |
| Final | 53.5 | 1.00 | 166 | 0.0868 | 1.3607 | 1.3607 | 210 |

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## 9.3 Statistical Consideration for Secondary Objectives

The secondary endpoints of this study include percent change in PSA from baseline to week 12 of treatment, maximum decline in PSA while on treatment, time to PSA progression, radiographic response, overall survival (OS) and toxicity of the combination treatment.

PSA level will be assessed at baseline, every 3 weeks for the first 18 weeks and every 6 weeks thereafter. The percent change in PSA from baseline to 12 weeks and the maximum change in PSA from baseline while on treatment will be compared between the two arms using Wilcoxon rank sum test. With 105 patients per arm, there will be 90% power to detect an effect size of 0.37, assuming one-sided type I error of 0.1. PSA progression will be assessed based on the definition in Section 6.2.1. Time to PSA progression is defined as the time from randomization to PSA progression. Patients without documented PSA progression will be censored at the last disease assessment. The distribution of time to PSA progression will be estimated using the Kaplan-Meier method. Stratified log rank test will be used to compare time to PSA progression between the two arms.

OS, defined as time from randomization to time of death or date last known alive, will be estimated for each arm using the Kaplan-Meier method and the stratified logrank test will be used to compare this endpoint across treatments. At the final analysis, the study will have 73% power to detect a hazard ratio of 0.67 with one-sided type I error of 0.1, assuming median OS of 36 months in the abiraterone acetate alone arm.

Another secondary endpoint of interest is radiographic response assessed per RECIST 1.1. Fisher's exact test will be used to compare the radiographic response rates between the two arms. Patients with radiographic response unknown or unevaluable will be considered as non-responders in this analysis.

Safety and tolerability of the study drugs be assessed by the CTCAE. All patients who receive treatment, regardless of eligibility, will be evaluated for toxicity and the percent of patients with various toxicities will be tabulated. The 90% confidence interval for the true probability of observing a toxicity of Grade 4 or higher in a given arm will be no wider than 17%. The probability of observing one or more toxicities among all 210 patients with a true rate of 1% is 88%. Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies.

Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.2.

## 9.4 Statistical Considerations for Exploratory Objectives

AR-V7 status will be assessed at baseline, at week 12 and at the time of disease progression. The proportion of AR-V7 positive patients at each time point will be summarized for each arm. The proportion of patients with AR-V7 status change at week 12 and disease progression will also be reported. To evaluate whether the addition of cabazitaxel would change the AR-V7 status among patients who are AR-V7 positive at baseline, Fisher's exact test will be used to compare the proportion of patients who become AR-V7 negative at follow-up assessments between the two arms among patients who are AR-V7 positive at baseline. Assuming 80% of patients will have sufficient samples for the AR-V7 analysis at both baseline and follow-up time points and 90% of samples will be delivered within 24 hours, there will be 75 analyzable patients in each arm for the analysis of AR-V7 status change. We anticipate about 15% of patients to be positive for AR-V7 at baseline and about 50% of these patients to convert to AR-V7 negative after receiving cabazitaxel. Assuming 11 (75*15%) patients with positive AR-V7 at baseline in each arm, the study has about 71% power to detect a difference in AR-V7 conversion rate of 50% vs. 10% between Arms A and B among AR-V7 positive patients using Fisher’s exact test with one-sided type I error of 0.15. Similar analysis will be performed to compare the proportion of patients who become AR-V7 positive at disease progression among those who are AR-V7 negative at baseline. Assuming 64 (75*85%) patients with negative AR-V7 at baseline in each arm, the study has about 80% power to detect a difference in AR-V7 conversion rate of 15% vs. 30% between Arms A and B among AR-V7 negative patients using Fisher’s exact test with one-sided type I error of 0.15. In addition, Cox regression will be used to evaluate the associations between baseline AR-V7 status and PFS as well as OS and its interaction with treatment.

9.5 Gender and Ethnicity

Based on previous data from **E3805** the anticipated accrual in subgroups defined by gender and race is:

| **Ethnic Category** | **Gender** | | |
|---|---|---|---|
| | **Females** | **Males** | **Total** |
| Hispanic or Latino | 0 | 12 | 12 |
| Not Hispanic or Latino | 0 | 198 | 198 |
| **Ethnic Category: Total of all subjects** | **0** | **210** | **210** |

| **Racial Category** | | | |
|---|---|---|---|
| American Indian or Alaskan Native | 0 | 0 | 0 |
| Asian | 0 | 3 | 3 |
| Black or African American | 0 | 23 | 23 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| White | 0 | 184 | 184 |
| **Racial Category: Total of all subjects** | **0** | **210** | **210** |

**The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.**

9.6 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Office – Boston.

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9.7 Tobacco Use Assessment

Detailed statistical considerations are outlined in Appendix VI

## 10. Imaging Research Study

All NaF PET/CT images are to be submitted via TRIAD as outlined in Section 4.6.4

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### 10.1 NaF PET/CT Imaging

The overall goal of this study is to examine whether the addition of cabazitaxel to abiraterone acetate can improve the overall response as well as the percentage of responding lesions compared to abiraterone acetate alone in support of our hypothesis. We expect a total of 50 eligible patients will be accrued in the sub-study. All participants will receive two imaging studies according to study protocol: pre-treatment NaF PET/CT at baseline and a mid-treatment NaF PET/CT at week 12**.** Eligible participants who have consented to this study will be actively involved in the trial and will be followed for treatment outcomes per protocol. NaF PET/CT image analysis will be performed at AIQ Solutions, Inc., using the FDA 510(K) cleared software

#### 10.1.1 Imaging Schedule

**Pre-treatment NaF PET/CT Imaging:** this imaging study should be completed prior to treatment start.

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**Mid-Treatment NaF PET/CT Imaging:** this imaging study should be completed during week 12 (day 85 +/- 7 days) of the study treatment.

#### 10.1.2 $^{18}$F-NaF Administered Dose

Place an intravenous catheter (IV), 18 or 20 gauge is preferred, in a vein of the participant's arm; inject $^{18}$F-fluoride (NaF) (0.14 mCi/kg of radiotracer up to a maximum of 10 mCi) into the IV in the participant's arm. A saline flush should follow the $^{18}$F-NaF injection. Perform a static whole body PET scan from mid-thigh to head after 60 minutes and CT attenuation correction scan;

**NOTE:** Imaging will take approximately 30 to 60 minutes, depending on the device and procedure for attenuation correction.

#### 10.1.3 Imaging Quality Assurance (QA)/Quality Control (QC) Procedure

Participant must be scanned on PET/CT scanners that have been qualified by the ACR Imaging Core Laboratory per the protocol-specific instructions made available to participating sites.

Qualification Utility for the Imaging Core Laboratory (QUIC) is the web-based tool for managing the qualification process and communicating with the core lab staff. The QUIC User Guide will be made available to participating sites.

Refer to the instructions about uploading images and completing the required application forms.

A hybrid PET/CT scanner is mandatory. The ability to calculate standardized uptake values (SUVs) is also mandatory. All sequential imaging sessions should be performed on the same PET/CT scanner, whenever possible. Any deviations should be reported to ECOG-ACRIN. QA/QC procedures will include review of DICOM files against study protocols. The PET/CT scanner must be kept calibrated in

accordance with the manufacturer's recommendations. The scanner should routinely be assessed for quantitative integrity and stability by being tested using various imaging protocols on a standard phantom. For SUV measurements, this assessment should include a comparison against a dose calibrator to ensure accuracy; that is, a comparison of the absolute activity measured versus the measured activity injected, should be performed.

A daily QC check must be performed at the beginning of the day, including PET/CT scanner and dose calibrator, in accordance with the manufacturer recommendations. If any of the QC results are outside of the manufacturer's guidelines, the study must be rescheduled and the problem rectified before scanning any patients.

10.1.4 Imaging Aims and Statistics

There are three imaging aims in this correlative study.

10.1.4.1 *To assess if the changes in total tumor burden from baseline to week 12 as assessed with NaF PET/CT will differ between two arms.*

For the imaging Aim 1, we assume the mean percentage of SUVtotal decrease was 30% in the abiraterone acetate alone arm [25, 27] and 60% (i.e., doubled) in the combination of cabazitaxel and abiraterone acetate arm, respectively, while the percentage of decrease is defined as (post SUVtotal – pre SUVtotal)/pre SUVtotal * 100%. The standard deviation was assumed to be 40% for both groups. Under the type I error 0.10 (two-sided), the sample size of 50 (25 in each arm) can achieve 83% power to detect the difference between two arms. Two-sample t-test assuming equal variance in PASS 14 was used for the computation.

10.1.4.2 *To correlate total tumor burden at baseline as assessed with NaF PET/CT with the PFS.*

For Aim 2, the total tumor burden is calculated as the sum of SUVtotal from all voxels and all lesions. The standard deviation at the baseline is assumed 6000 based on the data from the previous studies [26]. The association with PFS will be analyzed through Cox regression. Assuming the R-square of total tumor burden with other covariates is 0.1, the sample size of 50 can achieve 1.0 power to detect a hazard ratio of 1.1 with 1 unit change of total tumor burden, when the event rate is anticipated 0.50. The power remains 1.0 when the event rate is 0.30 or 0.70. A two-sided Cox regression with 0.05 significance level in PASS 14 was used for the computation. The other covariates in the Cox regression include age, performance status, clinical stage and treatment arm.

10.1.4.3 *To correlate heterogeneity of response from baseline to week 12 as assessed with NaF PET/CT with the PFS.*

For the imaging Aim 3, the heterogeneity of response is defined as the standard deviation of SUVmean from all lesions. The standard deviation of difference from baseline to week 12 is assumed 3.5 based on the data from the previous studies [26]. The association with PFS will be analyzed through Cox regression. Assuming the R-square of the heterogeneity of response with other covariates is 0.1, the sample size of 50 can achieve 0.86 power to detect a hazard ratio of 1.2 with 1 unite change, when the event rate is anticipated 0.50. The power is 0.65 or 0.95 when the event rate is 0.30 or 0.70, respectively. A two-sided Cox regression with 0.05 significance level in PASS 14 was used for the computation. The other covariates in the Cox regression include age, performance status, clinical stage and treatment arm.

## 11. Submission of Biospecimens for Research

Peripheral blood is to be submitted from consenting patients for defined laboratory research studies and/or undefined research.

It is required that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (see Section 11.4). An STS shipping manifest form is to be included with every submission.

All specimens must be labeled clearly with the ECOG-ACRIN protocol number (EA8153), ECOG-ACRIN patient sequence number, patient's initials, date and time of specimen collection, time point and specimen type.

### 11.1 Sample Collection and Submission Schedule

Kits for the collection and shipment of the peripheral blood specimens are ordered on-line from Cenetron Central Laboratories. Instructions are provided in Appendix IV. Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000. Kits must be ordered after the patient has been randomized to the trial and will generally arrive within three (3) business days from when the order was placed.

Specimens are to be submitted as follows:

- Peripheral blood specimens are to be submitted per patient consent as outlined in Sections 11.2 and 11.3. Blood specimens are to be collected at the following time points for each tube type:
  - Prior to Start of Treatment
  - Week 12
  - Time of Disease Progression

### 11.2 Submissions to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF)

If you have any questions concerning specimen collection and shipment, please contact the ECOG-ACRIN CBPF at (844) 744-2420.

#### 11.2.1 Peripheral Blood Submissions

Submit from patients who answer "Yes" to "I agree to provide additional blood for research."

Peripheral blood is to be collected as outlined in Section 11.1

##### 11.2.1.1 Specimen Preparation Guidelines

Streck Tubes

- Draw two (2) 10mL Streck Cell-Free DNA BCT tubes of blood at each time point.
- Ensure that at least 10mL of blood is drawn into each tube. Avoid low volume to minimize agitation during shipping.
- Invert the tubes gently 180 degrees and back 8-10 times.

- Maintain blood at room temperature (6°C to 37°C) until shipping. **Do Not** place tubes in refrigerator.

11.2.2 Shipping Procedures

Peripheral blood specimens are to be shipped at ambient temperature Monday-Thursday via overnight courier.

**Friday shipments are ill advised, similarly shipping before holidays is often problematic. The laboratory is closed Saturday, Sunday, and holidays.**

Ship using the CBPF's FedEx account using the FedEx on-line ship manager.

Ship to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3598
1515 Holcombe Boulevard
Houston, TX 77030
Phone: Toll Free (844) 744-2420 (713-745-4440 Local or International Sites)
Fax: (713) 563-6506
Email: eacbpf@mdanderson.org

Access to the FedEx shipping account for shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center can only be obtained by logging onto fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org

An STS shipping manifest form must be generated and shipped with all specimen submissions.

11.3 Submissions to Johns Hopkins University

If you have any questions concerning specimen collection and shipment, please contact Jun Luo at (443) 287-5625.

11.3.1 Peripheral Blood Submissions

Submit from patients who answer "Yes" to "I agree to have my samples collected and I agree that my samples and related information may be used for the laboratory studies."

Peripheral blood is to be collected as outlined in Section 11.1

11.3.1.1 Specimen Preparation Guidelines

ACD Yellow Top Tubes

- Draw two (2) 8.5mL Solution A Vacutainer tubes of blood at each time point.

- Ensure that at least 8.5mL of blood is drawn into each tube. Avoid low volume to minimize agitation during shipping.
- Invert the tubes gently 180 degrees and back 3-4 times.
- Store blood refrigerated at 4°C to 8°C until shipping. Do not put on ice. Do not leave blood refrigerated overnight. Ship blood the day of collection.

11.3.2 Shipping Procedures

Peripheral blood specimens are to be shipped the same day they are drawn Monday-Thursday via overnight courier.

**Friday shipments are ill advised, similarly shipping before holidays is often problematic. The laboratory is closed Saturday, Sunday, and holidays.**

Activate the NanoCool shipper and place the tubes wrapped in bubble wrap (or inserted into plastic tube holders) snugly in the shipping box.

Ship using the CBPF's FedEx account using the FedEx on-line ship manager.

Notify Dr. Luo's laboratory of the tracking number on the day of shipment by emailing jluo1@jhmi.edu

Ship to:
Jun Luo, Ph.D.
411 Marburg, Johns Hopkins Hospital
6100 N. Wolfe Street
Baltimore, MD 21287
Tel: (443) 287-5626
Email: jluo1@jhmi.edu

An STS shipping manifest form must be generated and shipped with all specimen submissions.

11.4 ECOG-ACRIN Sample Tracking System

It is **required** that all specimens 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 specimens required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

**Important:** 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 form should be shipped with all specimen submissions.

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

**Study Specific Notes**

Generic Specimen Submission Form (#2981v3) will be required only if STS is unavailable at time of specimen submission. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory.

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

11.5 Use of Specimens in Research

Specimens from patients who consented to allow their specimens to be used for future undefined ECOG-ACRIN approved research studies will be retained in an ECOG-ACRIN designated central repository.

For this trial, specimens will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility.

Specimens submitted will be processed to maximize their utility for current and future research projects. DNA, RNA, serum, and plasma (if appropriate) will be isolated from the submitted peripheral blood specimens.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future research study. Specimens will be destroyed per guidelines of the respective repository.

11.6 Sample Inventory Submission Guidelines

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

## 12. Laboratory Research Studies

Results of these studies are for the purposes of the trial only and will not be returned to the site or reported to the patient.

### 12.1 Association of Androgen-Receptor Splice Variant 7 Messenger RNA (AR-V7) Presence in Circulating Tumor Cells and Response to Treatment and Outcome

It has been shown that the detection of androgen-receptor splice variant 7 messenger RNA (AR-V7) in circulating tumor cells from patients with CRPC is associated with resistance to abiraterone acetate and enzalutamide, whereas it is not associated with resistance to taxanes [18, 19]. In an initial study, a total of 31 patients treated with enzalutamide and 31 patients treated with abiraterone acetate were prospectively evaluated for the presence of AR-V7, which was detected in 39% and 19%, respectively [18]. Among patients receiving abiraterone acetate, AR-V7 positivity was associated with lower PSA response rate (0% vs. 68%; p=0.004), and shorter PSA PFS (1.3 months vs. not reached; p<0.001), clinical or radiographic PFS (2.3 months vs. not reached; p<0.001) and OS (10.6 months vs. not reached; p=0.006). However, in patients treated with taxanes, it appears that the presence of AR-V7 does not confer resistance to treatment [19]. From the 37 taxane-treated patients, 17 (46%) were tested positive for AR-V7. Both AR-V7 positive and negative patients had similar responses to therapies, assessed both by PSA and radiographically. A pooled analysis of patients from both studies showed that outcomes were superior with taxanes compared to enzalutamide or abiraterone acetate in AR-V7-positive men (PSA responses 41% vs. 0%; p<0.001), PSA PFS (HR 0.19; 95% CI 0.07-0.52; p=0.001) and radiographic PFS (HR 0.21; 95% CI 0.007-0.59; p=0.003).

Our aim is to prospectively examine: a) whether patients positive for AR-V7 at baseline have a longer radiographic or clinical PFS to the combination of cabazitaxel and abiraterone acetate vs. abiraterone acetate alone; b) whether the addition of cabazitaxel can change the AR-V7 status of patients who are positive at study registration; and c) whether the addition of cabazitaxel to abiraterone acetate has any impact on future development of AR-V7 positivity at the time of disease progression. PFS is again defined as time from randomization to radiographic or clinical progression or death without progression. AR-V7 status at baseline, at 12 weeks into treatment and at the time of disease progression will be analyzed and the proportion of AR-V7 positive patients will be summarized for each arm. The proportion of patients with AR-V7 status change at 12 weeks and disease progression will also be reported. In addition, Cox regression will be used to evaluate the associations between AR-V7 status and PFS as well as OS and its interaction with treatment.

### 12.2 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secure 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.

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## 13. Electronic Data Capture

Please refer to the **EA8153** Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave and EASEE-PRO (for tobacco use assessment).

This study will be monitored by the Clinical 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.

## 14. Patient Consent and Peer Judgment

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

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**Cabazitaxel with Abiraterone versus Abiraterone alone Randomized Trial for Extensive Disease following Docetaxel: the CHAARTED2 Trial**

## Appendix I

## 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 research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me 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]

**Cabazitaxel with Abiraterone versus Abiraterone alone Randomized Trial for Extensive Disease following Docetaxel: the CHAARTED2 Trial**

## Appendix II

## Patient Pill Calendar

### Pill Calendar Directions

1. Take your scheduled dose of each pill.
2. If you forget, the missed pills will not be taken later.
3. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.

## Patient Pill Calendar: Abiraterone acetate

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each pill. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

**NOTE:** Abiraterone acetate is taken once daily, continuously, on an empty stomach 2 hours before or after meals. Abiraterone acetate is to be taken whole tablets with water. Do not crush or chew tablets.

**NOTE:** As prednisone must be taken with food, you **can not** take abiraterone acetate and prednisone together.

| **Patient ID:** | | | | | | **Agent Name: Abiraterone acetate** | | |
|---|---|---|---|---|---|---|---|---|
| Rev. Add#3 | **Date** | | | **Time pills taken** | | **Number of pills taken** | | **Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)** |
| **DAY** | **Month** | **Day** | **Year** | **AM** | **PM** | | | |
| 1 | | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 | | | | | | | | |
| 5 | | | | | | | | |
| 6 | | | | | | | | |
| 7 | | | | | | | | |
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| 22 | | | | | | | | |

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| **Patient ID:** | | | | | | **Agent Name: Abiraterone acetate** | | |
|---|---|---|---|---|---|---|---|---|
| **DAY** | **Date** **Month** | **Day** | **Year** | **Time pills taken** **AM** | **PM** | **Number of pills taken** | | **Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)** |
| 23 | | | | | | | | |
| 24 | | | | | | | | |
| 25 | | | | | | | | |
| 26 | | | | | | | | |
| 27 | | | | | | | | |
| 28 | | | | | | | | |

Investigator Signature: _____ Investigator Date: _____

## Patient Pill Calendar: Prednisone

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each pill. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

**NOTE:** Prednisone is taken twice daily, continuously, with food.

**NOTE:** As abiraterone acetate must be taken on an empty stomach, you **cannot** take abiraterone acetate and prednisone together.

| **Patient ID:** | | | | | | **Agent Name: Prednisone** | | |
|---|---|---|---|---|---|---|---|---|
| | **Date** | | | **Time pills taken** | | **Number of pills taken** | | **Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)** |
| **DAY** | **Month** | **Day** | **Year** | **AM** | **PM** | **AM** | **PM** | |
| 1 | | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 | | | | | | | | |
| 5 | | | | | | | | |
| 6 | | | | | | | | |
| 7 | | | | | | | | |
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| 22 | | | | | | | | |
| 23 | | | | | | | | |
| 24 | | | | | | | | |

| **Patient ID:** | | | | | | **Agent Name: Prednisone** | | |
|---|---|---|---|---|---|---|---|---|
| **DAY** | **Date** **Month** | **Day** | **Year** | **Time pills taken** **AM** | **PM** | **Number of pills taken** **AM** | **PM** | **Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)** |
| 25 | | | | | | | | |
| 26 | | | | | | | | |
| 27 | | | | | | | | |
| 28 | | | | | | | | |

Investigator Signature: _____ Investigator Date: _____

**Cabazitaxel with Abiraterone versus Abiraterone alone Randomized Trial for Extensive Disease following Docetaxel: the CHAARTED2 Trial**

## Appendix III

## ECOG Performance Status

| | |
|---|---|
| **PS 0** | Fully active, able to carry on all pre-disease performance without restriction |
| **PS 1** | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work. |
| **PS 2** | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| **PS 3** | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| **PS 4** | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |

**Cabazitaxel with Abiraterone versus Abiraterone alone Randomized Trial for Extensive Disease following Docetaxel: the CHAARTED2 Trial**

## Appendix IV

### EA8153 Collection and Shipping Kit Order Instructions

Specimen Collection/Shipping Kits are being provided by CENETRON CENTRAL LABORATORIES and are to be ordered ONLINE.

Starter kits are not available. Kit requests are to be made AFTER patient randomization.

Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron clinical trials group at (512) 439-2000.

Ordering Process:

- At time of patient randomization, provide the contact for kit ordering in OPEN
- Following randomization of the patient to the trial, go to the website www.cenetron.com and click on the 'Order Kits' button at the top right. It is recommended that kits be ordered same day as patient randomization.
- The order form is not study specific and can be used for any study. Complete the online form as follows:
    - **Sponsor (REQUIRED):** ECOG-ACRIN
    - **Contact Name (REQUIRED):** Name of the site kit contact. Should match the name of the individual provided in OPEN as the kit contact
    - **Protocol Number (REQUIRED):** EA8153
    - **Phone Number (REQUIRED):** Phone number of the kit contact. Please ensure that this is a number that can be reached from an external caller
    - **Site Number (REQUIRED):** Institution NCI Site ID
    - **FAX Number:** Fax number of the kit contact
    - **Investigator:** Last name of the kit contact is adequate
    - **Email (REQUIRED):** Email of the site kit contact. Must be entered twice to confirm
    - **Date Supplies Needed (REQUIRED):** Add three (3) business days or more to order date. (E.g. if ordering on 2/5/2016, indicate 2/10/2016 to accommodate the weekend. Reminder that holidays must also be considered in this timeline)
    - **KIT NAME (REQUIRED):** EA8153 Collection Kit
    - **Quantity:** 1
    - **Comments:** Provide EA8153 Patient Case ID# and full shipping address
        - 'Patient Case ID =' #####
        - *'Ship Kit to'* name of the individual to whom the kit is being shipped. (May be different than the kit contact provided above)
        - Full street address, town, state and zip code
    - Answer the security question

**Please complete this form correctly, including the valid ECOG-ACRIN patient case number and complete shipping address. If information is missing the kit processing will be delayed.**

**Cabazitaxel with Abiraterone versus Abiraterone alone Randomized Trial for Extensive Disease following Docetaxel: the CHAARTED2 Trial**

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## Appendix V

### EA8153 Cabazitaxel Study Drug Request Form and EA8153 Investigational Product Destruction Record Download Instructions

Downloading the EA8153 Cabazitaxel Study Drug Request Form and EA8153 Investigational Product Destruction Record: These forms are available for download from the EA8153 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the ECOG-ACRIN link to expand, then select trial protocol EA8153
- Click on Documents tab, select the Pharmacy tab, and download and complete the forms provided.

**Cabazitaxel with Abiraterone versus Abiraterone alone Randomized Trial for Extensive Disease following Docetaxel: the CHAARTED2 Trial**

## Appendix VI

Rev. Add#2

## Ancillary for Tobacco Use Assessment: EAQ16T

Study Co-Chairs: Elyse Park, Ilana Gareen, Lynne Wagner, Jamie Ostroff, Ben Herman

Patients registered to selected ECOG-ACRIN trials are eligible to participate in this ancillary study, once the appropriate amendment incorporating the study is activated.

The Ancillary for Tobacco Use Assessment is a project that seeks to address questions about patient-reported tobacco use and smoking behaviors that may span several studies and/or diseases. The tobacco use ancillary is embedded into parent protocols, with participation in the ancillary informed in the parent consent form and participation determined via providing email address to the sites. The general objectives of the tobacco use ancillary are not specific to any single parent protocol; however, specific objectives may be included in the parent or related parent protocols.

A significant proportion of cancer patients are current smokers at the time of cancer diagnosis,[1–5] and there are known risks associated with continued smoking following cancer diagnosis. These include decreased survival time; increased complications from surgery, radiation, and chemotherapy; and increased risk of second primary tumors.[6–11] As such, the National Comprehensive Cancer Network (NCCN), the American Association of Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) have identified persistent smoking as a modifiable risk factor and recommend cessation counseling for cancer patients who smoke. Although evidence-based guidelines for treating tobacco dependence exist,[12] they have not yet been well-integrated into cancer care settings. Moreover, knowledge regarding the scope and patterns of tobacco use among cancer patients is limited. As a critical step in closing this knowledge gap, the NCI-AACR Cancer Patient Tobacco Use Asssessment Task Force developed the Cancer Patient Tobacco Use [1–4,13,14] Questionnaire (C-TUQ). Through this ancillary, the modified C-TUQ measures will be administered to participants enrolling in selected Phase II and Phase III ECOG ACRIN (EA) therapeutic trials.

The major questions may be summarized:

1. What is the smoking status of cancer patients enrolled on EA clinical trials?
2. Do patients quit smoking or try to quit smoking after receiving a cancer diagnosis?
3. What forms of tobacco use do patients engage in?
4. What assistance do patients use or receive to try to quit?
5. How does tobacco use, other forms of tobacco use, and/or environmental tobacco exposure affect patient's treatment toxicity, patient-reported physical and psychological symptoms, trial adherence, and therapeutic outcomes?

When patients consent to participate, they will be asked to provide a contact email address and that address along with their registration information will be sent directly from the parent trial's registration system to ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO), and the patient will be automatically registered into EASEE-PRO for participation. To activate their account for self-directed web entry of surveys, the system will send an activation message to the contact email address that will explain how to activate their account for self-directed web entry of surveys. After their account is activated, the patient will

be able to complete questionnaires using a secure browser interface from any web enabled computer, tablet, or mobile device.

Measures

The selected Core and Extension C-TUQ items will be assessed. The 4-item Short Form PROMIS® for anxiety and depression, the Lung Cancer Stigma Scale, and six symptom items (general pain, fatigue, nausea, cough, insomnia, shortness of breath) from FACIT (Functional Assessment of Chronic Illness Therapy)) together with modifications of these same six questions to address the degree of bother associated with each symptom will be administered as well. Additionally, we will ask participants' perceptions of how smoking improves or worsens each of the six symptom experience. All these items will be compiled into Survey of Tobacco Use (STU) (baseline and follow-up).

Contents and Corresponding Questions in Survey of Tobacco Use (STU)

| Dimension | Source of Measures | Baseline STU | Follow-up STU |
|---|---|---|---|
| Basic Tobacco Use Information | C-TUQ | Q1 – Q5 | Q1 – Q2 |
| Tobacco Use in Relation to Cancer Diagnosis and Treatment | C-TUQ | Q6 – Q7 | Q3 |
| Smoking Cessation, Cessation Products, and Assistance Methods | C-TUQ | Q8 – Q13 | Q4 – Q9 |
| Use of Other Products | C-TUQ | Q14 | Q10 |
| Second-Hand Smoke Exposure | C-TUQ | Q15 – Q16 | Q11 – Q12 |
| Psychological Symptoms | PROMIS<br>Lung Cancer Stigma Scale | Q17 – Q18 | Q13 – Q14 |
| Physical Symptoms | FACIT | Q19 | Q15 |
| Sociodemographics | | Q20 – 21 | |

**NOTE:** In order to minimize ambiguity and assure that patients are oriented to answer appropriately, the specific phrasing of items may vary depending specific cancer type and treatment.

**Tobacco Use**. The selected Core and Extension C-TUQ items (from categories of Basic Tobacco Use Information, Tobacco Use in Relation to Cancer Diagnosis and Treatment, Smoking Cessation/Cessation Products/Assistance Methods, Use of Other Products, and Second-Hand Smoke Exposure) will be assessed in the baseline and follow-up Survey of Tobacco Use.

**Oncology Provider Assistance**. C-TUQ Question 13 assesses "cancer doctors" Advise. We will add 4 As to assess participants' reported 5As (Ask (Q12a), Advise (Q12b), Assess (Q12c), Assist (Q12d-Q12f), and Arrange follow-up (Q12g), as in Baseline STU).[80]

**Psychological Symptom Assessment.** Anxiety & Depression: *(The Patient Reported Outcomes Measurement Information System (PROMIS®)).* We will administer the 4-item Short Form PROMIS® for anxiety and depression (Q17 in Baseline STU). Stigma: The Lung Cancer Stigma scale measures the extent to which shame is internalized (Q18 in Baseline STU).[81]

**Physical Symptom Assessment** *Physical Symptom Assessment (Functional Assessment of Chronic Illness Therapy (FACIT)). FACIT, a measurement system with a collection of quality-of-life questionnaires, expands the more familiar FACT (Functional Assessment of Cancer Therapy) questionnaires into other chronic illness and conditions. FACIT consists of many*

*individual questions to assess various symptoms from the patient perspective. We will use 6 FACIT items, selected based on the therapeutic regimens, expected toxicity, and malignancy type of the parent trials. In addition, we have created modifications of these same six questions to address the degree of bother associated with each symptom" The symptoms of general pain, fatigue, nausea, cough, sleep difficulty, and shortness of breath will be assessed, first using the standard and validated FACT item, and then asking the degree of "bother" imposed by each symptom, on the same 5-point scale. These clusters of symptoms were specifically chosen based on potential interactions between tobacco use and longitudinal symptoms.*

**Sociodemographic Variables.** Sociodemographic variables, including age, sex, zip code, and race/ethnicity are collected for all NCTN trial participants at registration. At baseline, participants will provide information on marital status (Q20 in Baseline STU) and education level (Q21 in Baseline STU) as part of the tobacco supplemental assessment.

**Cancer Treatment Variables**. Clinical variables including date of diagnosis, malignancy type (smoking related vs. non-smoking related, cancer stage), and treatment details (i.e. types and dates of surgery, chemotherapy, and/or radiation received), along with disease status and survival, will be captured in Medidata Rave via the parent protocol and will be available for analysis of the ancillary. Provider-assessed adverse events will also be captured via the parent protocol in Medidata Rave, using case report forms commonly used across the NCTN and using standard data elements.

Assessments

All items in Survey of Tobacco Use will be administered using the EASEE-PRO system. The advantage of our virtual electronic data capture system is that our proposed assessments will not be limited to, or dependent upon, patient trial visits. Confidential and potentially stigmatizing information can be provided without requiring direct contact with the care team.

Timing of Assessments

Given the critical questions that remain[13] about the timing of conducting tobacco use assessments, we have carefully chosen to collect tobacco assessment data at trial enrollment, 3 and 6 month follow-up. For tobacco treatment trials, 6 month follow-up is the recommended primary outcome time point. By 6 month follow-up, most cancer treatment-related quitting activity[62], cancer treatment initiation of therapy, and FDA-approved smoking cessation medication regimens will be completed. Adverse events during treatment will have been observed.

Statistical Considerations and Analysis Plans

The analysis plans described below are planned for a combined analysis of the data from the 8 selected ECOG-ACRIN trials. Consistency in the effects over the studies would be examined in this analysis.

1. CHANGES IN SMOKING STATUS AND EXPOSURE. At baseline, combustible tobacco use (1a) will be characterized by smoking status (never smoker, former smoker, and current smoker based on Baseline STU Qs 1 and 5), other forms of tobacco use (1b) will be a composite variable determined by non-cigarette items (based on Baseline STU Q7 and Q14), and environmental tobacco smoke (ETS) level (1c) will be determined by current household and work exposure (Baseline STU Qs 15-16). At follow-up, combustible tobacco use (1a) will be examined by smoking status (Follow-up STU Qs 1 and 2), other forms of tobacco use (1b) will be determined by Follow-up STU Q10, and ETS level (1c) will be determined by 30 day household and work exposure (Follow-up STU Qs 11-12). We will examine tobacco use at baseline, 3 and 6 month follow-up, and change in status (abstinence in combustible tobacco, abstinence of other forms of tobacco use, and change

in exposure to smoke-free home and work) using summary statistics (frequency and proportion). We will explore the effects of sociodemographic and cancer treatment factors on smoking status using logistic regression (comparing smokers and non-smokers). We will also evaluate factors associated with changes in smoking status.

2. TREATMENT TOXICITY. The selected trials capture information about adverse events during treatment using NCI's Common Terminology Criteria for Adverse Events, Version 4. Toxicities are measured at each treatment visit and graded according to severity, with grade 1 corresponding to mild toxicity and grade 5 signifying a lethal adverse event. We will determine each patient's worst degree toxicity across all event types and treatment visits and will compare the distribution of worst degree grades between smokers and non-smokers and between patients with environmental tobacco exposure and those without exposure using exact tests. We will also examine the distribution of worst degree grades between users with different form of tobacco use. In addition, we will explore the effects of tobacco use on dose modifications (yes vs. no) using logistic regression, with each patient's dose modification status determined across all treatment visits.
3. SYMPTOM BURDEN. Tobacco variables will be conceptualized as described in the section of CHANGES IN SMOKING STATUS AND EXPOSURE. Tobacco use status (as measured at baseline, 3 and 6 month follow-up) will be compared to physical and psychological symptom burden (as measured at each corresponding time points). At 3 and 6 month follow-up, we will also examine the association between tobacco use changes and changes in symptom burden. We will explore the effects of sociodemographic and cancer treatment factors on symptom burden using repeated measures mixed effects models. As an example of statistical power, we consider the PROMIS SF-4 depression measure. We assume that 1500 patients will be enrolled across the 8 parent studies over 13 months, and that 20% are smokers. We assume that 85% of patients will have assessments at 6 months. Given groups of these sizes (26 quitters and 230 still-smokers) and standard deviation of 4.08 for the PROMIS SF-4 depression scale, there will be 83% power to detect a difference in change scores of 2.5 between groups using a two-sample t-test with Type I error of 5%. The minimally important difference for this instrument is 2.2.[79]
4. CESSATION PATTERNS AND TREATMENT. At baseline we will explore pre-treatment combustible tobacco use patterns (STU Q6a and Q6b), quitting behaviors (STU Q13), behavioral program utilization (STU Q11) and oncology provider support (5As, STU Q12), and smoking cessation medication use (STU Q10). At follow-up we will explore post-treatment combustible tobacco use patterns (STU Q3a-Q3e), quitting behaviors (STU Q9), behavioral program utilization (STU, Q7) and oncology provider support (5As, STU Q8), and smoking cessation medication use (STU Q6). We will explore the effects of sociodemographic and cancer treatment factors on these variables. We will examine associations of quitting behaviors and behavioral and medication utilization with tobacco use status (as outlined in the section of CHANGES IN SMOKING STATUS AND EXPOSURE) at baseline and on respective 3 and 6 month tobacco outcomes. These analyses will be descriptive in nature. Summary statistics (frequency, proportions, and 95% confidence intervals) will be used.
5. TRIAL OUTCOMES. We will compare treatment duration between smokers and non-smokers and between patients with environmental tobacco exposure and those without exposure. Cumulative incidence/competing risk methods will be used to estimate time to treatment discontinuation for adverse events, disease progression, completion per protocol, or other causes. Gray's test will be used to test for differences in the cumulative incidence distributions.[78] Differences in the distribution of reasons for discontinuation of treatment will be examined using exact tests. Relative dose intensity is defined as the ratio of actually delivered dose intensity to the planned dose intensity. The effects of tobacco use and

exposure on relative dose intensity (≥ 90% vs. < 90%) will be explored using logistic regression. Differences in the primary endpoint and important secondary endpoints will be examined using log rank test and exact test (as appropriate).

Data collected in the tobacco use project will support a range of analyses. Precise estimates of power will depend on the prevalence of smoking at baseline among study participants, the proportion whose smoking status changes, and the duration and adequacy of follow-up.

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