Protocol version 6.0 dated April 3, 2020

NCT #:NCT03069937

MUSC CTO #: 102509

A PHASE II STUDY OF DOCETAXEL BEFORE MEDICAL CASTRATION WITH DEGARELIX IN PATIENTS WITH NEWLY DIAGNOSED METASTATIC PROSTATIC ADENOCARCINOMA.

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PROTOCOL VERSTION HISTORY
Version 6.0 dated April 3, 2020
Version 5.0 dated February 19, 2019
Version 4.0 dated September 18, 2018
Version 3.2 dated July 6, 2018
Version 2.1 dated March 27, 2017
Version 1.1 dated 12/13/2016
Version 1 dated 11/30/16

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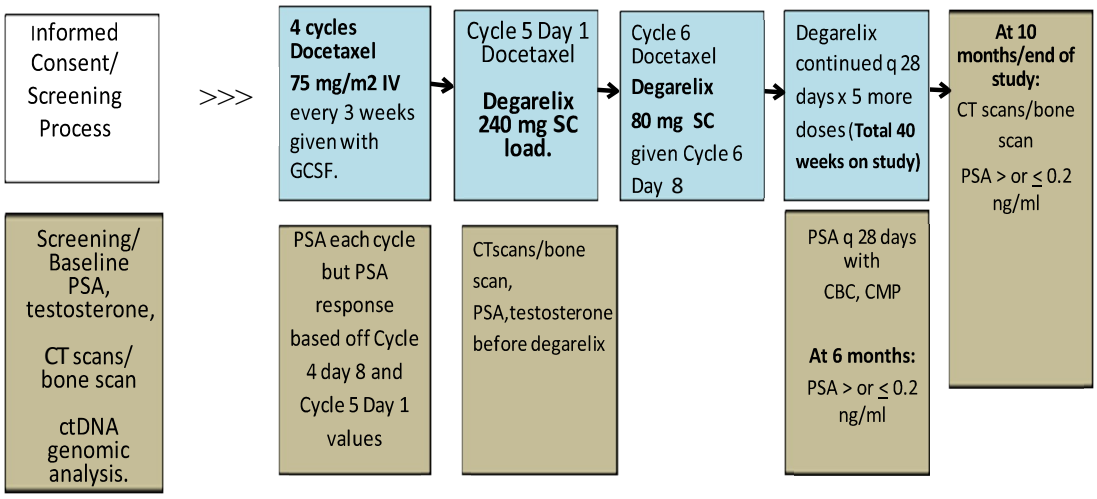
1 SCHEMA


Informed Consent/ Screening Process
>>>
4 cycles Docetaxel 75 mg/m2 IV every 3 weeks given with GCSF.
Cycle 5 Day 1 Docetaxel
Degarelix 240 mg SC load.
Cycle 6 Docetaxel
Degarelix 80 mg SC given Cycle 6 Day 8
Degarelix continued q 28 days x 5 more doses (Total 40 weeks on study)
At 10 months/end of study:
CT scans/bone scan
PSA > or ≤ 0.2 ng/ml
Screening/ Baseline PSA, testosterone,
CT scans/ bone scan
ctDNA genomic analysis.
PSA each cycle but PSA response based off Cycle 4 day 8 and Cycle 5 Day 1 values
CTscans/bone scan, PSA,testosterone before degarelix
PSA q 28 days with CBC, CMP
At 6 months:
PSA > or ≤ 0.2 ng/ml

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

- The primary objective of this study is to determine the proportion of men with newly diagnosed metastatic hormone sensitive prostate cancer who obtain and maintain a PSA complete response (less than or equal to 0.2 ng/ml) at 10 months (40 weeks) after initiation of trial therapy (7 months of androgen deprivation therapy) with four cycles of upfront docetaxel chemotherapy without androgen deprivation therapy followed by two additional cycles of docetaxel concurrent with androgen deprivation therapy with LHRH antagonist degarelix and then ongoing degarelix.

2.2 SECONDARY OBJECTIVES

- To determine the proportion of men with newly diagnosed metastatic hormone sensitive prostate cancer who obtain and maintain a PSA complete response (less than or equal to 0.2 ng/ml) at 6 months (28 weeks) after initiation of trial therapy with four cycles of upfront docetaxel chemotherapy without androgen deprivation therapy followed by two additional cycles of docetaxel concurrent with androgen deprivation therapy with LHRH antagonist degarelix and then ongoing degarelix.
- To assess the toxicity of administering four cycles of docetaxel chemotherapy without androgen deprivation therapy followed by two additional cycles of docetaxel concurrent with androgen deprivation therapy with degarelix in non-castrate men with newly diagnosed metastatic hormone-sensitive prostate cancer.
- To determine the frequency of disease progression (clinical, radiographic, or PSA as outlined in this protocol), if any, during the four cycles of upfront docetaxel.
- To determine the frequency of PSA response during the four cycles of upfront docetaxel.
- To determine the time to development of castration resistance after initiation of ADT with degarelix for the cohort as a whole during the entire course of therapy.
  To determine the progression-free survival and overall survival of the patients treated with upfront docetaxel followed by ADT.

2.3 EXPORATORY OBJECTIVES

- To determine whether baseline tumoral genomic changes assessed via a serum assay of cell-free tumor DNA correlate with responses to trial therapy.
- To evaluate PSA kinetics over time over the duration of study therapy.

3 BACKGROUND

3.1 METASTATIC PROSTATE CANCER

Prostate cancer is the second-leading cause of cancer-related death in men in the United States. The American Cancer Society estimates that 220,800 cases of prostate cancer were diagnosed in the U.S. in 2015 with 27,540 deaths from the disease.(1) Prostate cancer with metastases, whether diagnosed as metastatic at presentation or progressing after previous

local therapy, is an incurable disease. A majority of patients with metastatic prostate cancer achieve an initial response to androgen deprivation therapy (ADT) and traditionally have been treated with LHRH agonist or orchiectomy plus or minus an antiandrogen. Unfortunately, castration resistant disease almost inevitably develops at an average of 18-24 months (2). Upon development of castration resistance, patients are eligible for palliative docetaxel chemotherapy or recently approved second-line hormonal therapies. It is only in the last few years that evidence has emerged to show a survival benefit to earlier initiation of docetaxel chemotherapy in combination with ADT before a patient's metastatic prostate cancer develops castration resistance.(3) We intend to evaluate the safety and potential efficacy of treating patients with newly diagnosed metastatic prostate cancer even earlier with docetaxel, before they are even exposed to ADT.

3.2 DOCETAXEL BASED CHEMOTHERAPY FOR PROSTATE CANCER

3.2.1 The Established Role for Docetaxel

Based on two randomized controlled trials showing an associated overall survival benefit, Docetaxel (Taxotere®), a taxane microtubule inhibitor, has become the standard chemotherapy for metastatic castration resistant prostate cancer (mCRPC). In the Southwest Oncology Group (SWOG) 9916 trial, docetaxel 60 mg/m2 every 3 weeks plus estramustine 280 mg three times daily on days 1-5 was compared to mitoxantrone 12 mg/m2 every 3 weeks plus prednisone 5 mg twice daily in men with mCRPC. (4) Median overall survival, time to disease progression, and PSA response were all statistically improved with the docetaxel-based therapy. In the TAX327 trial, men with mCRPC were randomized to mitoxantrone 12mg/m2 every three weeks, docetaxel 75 mg/m2 every three weeks, or docetaxel 30 mg/m2 for five of every six weeks with all arms also receiving prednisone 5 mg twice daily.(5) Both docetaxel arms of the TAX327 trial demonstrated statistically significant increases in number of patients achieving a greater than 50 percent PSA response as compared to mitoxantrone. Docetaxel 75 mg/m2 every three weeks was the only arm to demonstrate a statistically significant overall survival benefit, 18.9 months, as compared to mitoxantrone, helping to firmly establish this drug and dosing schedule as the standard of care chemotherapy for mCRPC.

3.2.2 A Role for Docetaxel in Castration Sensitive Prostate Cancer

Three recent randomized controlled trials have evaluated the role of docetaxel for men with metastatic prostate cancer before the disease becomes castration-resistant. E3805 randomized 790 men with newly diagnosed metastatic hormone-sensitive prostate cancer to androgen deprivation therapy alone or ADT plus 6 cycles of docetaxel 75mg/m2 initiated within four months of initiation of ADT.(3) After a median follow-up of 28.9 months, median survival was significantly longer in the chemotherapy plus ADT group at 57.6 months vs. 44.0 months with ADT alone (HR for death in the combination group of 0.61; 95% confidence interval, 0.47-0.80; $p<0.001$). Patients were stratified prospectively into low-volume and high-volume disease with "high-volume" defined for that protocol as the presence of visceral disease or 4 or more bony lesions including at least one bony lesion outside of the vertebral column and bony pelvis. The increase in overall survival was even more significant in the combination therapy arm when analysis was restricted to patients with high-volume disease at 49.2 months as compared to 32.2 months in high volume patients who received ADT alone. (HR = 0.60; 95% CI, 0.45-

0.81; p=0.0006).(3) A statistically significant difference in overall survival has not yet been reached in low volume patients although HR for death in the combination therapy patients with low volume disease was remarkably similar to high volume patients at 0.63 (95 % CI 0.34-1.17; p = 0.1398.) Median time to disease progression for the E3805 cohort as a whole (based on radiographic criteria, PSA, or symptoms) was also significantly increased in the combined therapy group at 20.2 months as compared to 11.7 months in the ADT alone arm. (hazard ratio, 0.61; 95% CI, 0.51 to 0.72; P<0.001). Finally, percentage of patients with PSA level less than 0.2 ng/ml at twelve months was increased in the combination therapy group at 27.7% as compared to 16.8% in the ADT alone group. (p<0.001).

A similar European trial, GETUG-AFU 15, randomized 385 men with newly diagnosed hormone-sensitive metastatic prostate cancer at centers in France and Belgium to ADT plus Docetaxel 75 mg/m2 every three weeks for up to nine cycles or ADT alone. (6). The docetaxel was initiated within 60 days after starting ADT. Biochemical progression free survival (lack of PSA progression, clinical progression, or death) was statistically increased in the ADT plus docetaxel arm at 22.9 months vs. 12.9 months in the ADT alone arm (HR 0.72, 0.57-0.91; p = 0.005). Median overall survival was not statistically increased at 58.9 months in the combination therapy group versus 54.2 months in the ADT arm (HR 1.01, 95% CI 0.75-1.36; p=0.955). Differences in relative survival benefit between E3805 and GETUG-AFU 15 may be driven by differences in baseline volume of metastatic disease between the two cohorts. Recent updated analysis of the GETUG-AFU 15 data at median follow-up of 82.9 months was performed with retrospective assessment of tumor volume using the definitions of high and low volume disease set forth in E3805. (7) 47.5% of GETUG-AFU 15 patients had high volume disease at presentation by E3805 criteria as opposed to 65.1% of patients in E3805. In 183 high volume patients in the GET-AFU 15 study, median overall survival was 39 months in the ADT plus docetaxel arm and 35.1 months in the ADT alone arm (HR 0.80; 95% CI 0.6-1.2; p=.35), thus not yet reaching statistical significance but in an underpowered subset analysis.

The recently conducted STAMPEDE trial used an ambitious randomized multi-arm, multistage design to analyze the effect of adding one or a combination of several agents to standard ADT in hormone-sensitive advanced prostate cancer. (8). One arm of the trial added 6 cycles of docetaxel 75 mg/m2 every 3 weeks plus prednisone 10 mg daily to ADT in patients with locally advanced or metastatic hormone-sensitive disease. Recently published data summarizing a pre-planned subset analysis of metastatic patients showed a statistically significant increase in median survival in the M1 patients receiving docetaxel plus ADT of 60 months as compared to 45 months in M1 patients receiving ADT alone(HR = 0.76, 95% CI 0.62-0.92; p= 0.005). With these three recent data sets available, many practitioners have begun to treat patients with metastatic hormone-sensitive prostate cancer, especially with high volume disease, with upfront ADT plus docetaxel.

3.2.3 Toxicity of Docetaxel Chemotherapy in Hormone Sensitive versus Castration-Resistant Prostate Cancer

Cytotoxic chemotherapy inevitably has potential toxicity and docetaxel is no exception. In the TAX 327 study, 332 mCRPC patients were on the arm receiving docetaxel 75 mg/m2 every 3 weeks plus prednisone, and 32% of these patients had Grade 3 or 4 neutropenia with 3% febrile neutropenia and 0.3% treatment-related death. (5) Interestingly, there is a suggestion that perhaps toxicity was higher in both E3805 and GETUG-AFU 15 with patients newly initiated on ADT. Because data regarding prophylactic use of G-CSF or antibiotics on E3805 and GETUG-AFU 15 are incomplete, the relative toxicity observed on the trials is somewhat difficult to interpret. That said, the drug-related death rate on GETUG-AFU 15 was 2.1%, higher than the 0.3% observed during TAX 327. After 56% accrual to GETUG-AFU 15, there had been 41% Grade 3 or 4 neutropenia with 8% febrile neutropenia and four treatment related deaths prompting an addendum to the protocol from the data safety monitoring committee mandating G-CSF administration from days 5-10 of each cycle. This modification yielded a subsequent drop in the febrile neutropenia rate to 6% and no further treatment-related deaths. In E3805, the Grade 3 or 4 neutropenia rate was only 12% with 0.3% deaths, but the febrile neutropenia rate was 6% and 2% (8/397) of the patients on the combined treatment arm died with "cause unknown."(3).

It is problematic to compare toxicities across trials, but there are data to suggest a hypothetical mechanism for increased hematologic toxicity with docetaxel in men who are more naïve to medical castration. *Franke, RM et al.* examined the relative clearance of docetaxel in ten non-castrated and twenty castrated men with prostate cancer. (9) Docetaxel pharmacokinetics were significantly altered in the castrated men with an approximately 100% increase in docetaxel clearance and accordingly two-fold reduction in AUC as compared to the men who were not castrated. Human and rat-model data were presented to suggest a mechanism for this difference in clearance as increased hepatic uptake of docetaxel via increased anion transporter expression in the setting of castration. This study suggests greater systemic exposure to drug as a possible explanation for increased hematologic toxicity from docetaxel in the non-castrated or newly castrated state as compared to the castrated state, but it also suggests one possible rationale for greater efficacy of earlier docetaxel administration.

3.2.4 Evidence to Support Administering Docetaxel Independently from Androgen Deprivation

3.2.4.1 Breast Cancer Model

Hormone-receptor positive breast adenocarcinoma invokes similarities in management to prostatic adenocarcinoma in that both disease states are generally responsive to both hormonal manipulation and cytotoxic chemotherapy. As opposed to prostate cancer, the established paradigm in breast cancer is generally administering cytotoxic chemotherapy independently from hormonal manipulation. Pre-clinical data suggest a possible antagonistic effect of tamoxifen on chemotherapy cytotoxicity in breast cancer cell lines(10, 11) including evidence that tamoxifen places more tumor cells in G1 phase of the cell cycle when they would theoretically

be less sensitive to cytotoxic therapy.(12). A randomized phase III trial of 1558 postmenopausal women with resected node-positive hormone-receptor positive breast cancer prospectively evaluated disease-free survival with adjuvant cyclophosphamide, doxorubicin, and fluorouracil followed by 5 years of daily tamoxifen versus the same adjuvant chemotherapy given concurrently with tamoxifen. After a median 9 years of follow-up, the sequential therapy showed a strong trend toward improved DFS with HR of 0.84 (95% CI 0.70-1.01; p = 0.061). (13).

3.2.4.2 Evidence from Prostate Cancer Cell Lines

In vitro studies of androgen dependent prostate cancer cell lines have shown increased sensitivity to taxane-mediated cell death in response to androgen stimulation of the androgen receptor. In one series, androgen-dependent LNCaP prostate cancer cells showed decreased survival when cultured with steroid hormones and paclitaxel (25% survival) as compared to cells depleted of steroid hormone and then cultured with paclitaxel (55-60% survival). The mechanism for this finding was outlined as likely increased caspase-dependent apoptosis in the presence of p53 activation and cellular proliferation. (14). In a separate trial in LNCaP-bearing severe combined immunodeficient mice, tumor volume and tumor apoptosis were measured in response to castration alone, docetaxel alone, both interventions administered concurrently, and both interventions administered in different sequences. Docetaxel administered prior to castration yielded the longest delay in tumor growth of the studied interventions including a statistically significant improvement as compared to castration followed by docetaxel. (p=0.0003) (15).

3.2.4.3 Evidence in Prostate Cancer Trials

Building on animal models, there has been limited exploration of docetaxel administration in prostate cancer in the non-castrate state. *Rathkopf et al.* performed a phase II trial in 102 non-castrate men with progressive biochemically recurrent or metastatic hormone sensitive prostate cancer evaluating the concept of androgen cycling. Patients were treated prospectively in two cohorts with different dosing strategies of concurrent docetaxel and LHRH agonist plus testosterone administered toward the end of each cycle of docetaxel to facilitate each subsequent dose of docetaxel being given in the non-castrate state. Cohort one received six cycles of docetaxel 75 mg/m2 administered every 28 days with leuprolide 7.5 mg IM given on each Day 1 and topical testosterone administered on days 21-27. Cohort two received nine cycles of docetaxel 70 mg/m2 administered every 21 days with leuprolide 22.5 mg IM given every 12 weeks and topical testosterone administered on days 18-20 of each cycle of docetaxel. Only two patients had disease progression during the chemo-hormonal therapy. One of the endpoints on the trial was undetectable PSA at 18 months. None of the patients in cohort one met this endpoint but 13% of the patients in cohort two did. The febrile neutropenia rate was 14% and 18% in respective cohorts, higher than the rate traditionally seen in castrate-resistant disease and attributed to the approximately 50% reduction in docetaxel clearance measured in these non-castrate patients as compared to historical controls. The authors of this study concluded that the efficacy results of this trial and the high febrile neutropenia

rate did not warrant further study of androgen cycling. Of note, the patients on this trial did have median trough testosterone levels that were in the castrate range during portions of each cycle of docetaxel. In terms of toxicity, only eleven patients received growth factor support and only in response to neutropenic fever or recurrent grade 3 or 4 neutropenia. (16)

In a model similar in many ways to our proposed study, *Hussain et al.* treated 39 men with non-castrate level testosterone and increasing PSA after definitive therapy for localized prostate cancer (prostatectomy or radiation) with up to six cycles of docetaxel 70 mg/m2 every three weeks. (17) The cytotoxic chemotherapy was followed by total androgen blockade with LHRH agonist and bicalutamide for 12-20 months. Serum PSA decreased $\geq$ 50% in 48.5% of patients and $\geq$ 75% in 20% of patients with the docetaxel alone, and only one patient had increased PSA at the end of the docetaxel therapy. The majority of patients had PSA progression shortly after stopping ADT but 5/33 (15%) patients continued to have undetectable PSA at a median of 18.9 months after stopping ADT. Of note, only seven of the men on this study had radiographic evidence of metastatic disease at study enrollment but three of these men were in the group who continued to have undetectable PSA for a lengthy period of time despite regaining non-castrate level testosterone post-ADT. Grade 3 or 4 neutropenia occurred in 61.5% of the patients on this trial with five episodes of febrile neutropenia. This study demonstrates a series of patients with progressive prostate cancer treated with docetaxel before ADT with only a minimal rate of progressive disease during the chemotherapy. It also raises the question of potential efficacy of this intervention in a larger cohort of patients with overt metastatic disease.

3.3 RISK GROUPS/VOLUME OF MESTASTATIC DISEASE

Multiple attempts have been made to develop prognostic criteria for newly diagnosed metastatic prostate cancer. *Glass et al.* developed a prognostic model in 2003 using recursive partitioning of data from SWOG 8894, a randomized trial comparing orchiectomy plus flutamide versus orchiectomy plus placebo in men with newly diagnosed metastatic prostate cancer.(18, 19) Four factors had a major impact on outcome and could be used to divide patients into good, intermediate, and poor risk with 5 year survivals of 42%, 21%, and 9% respectively. These factors were appendicular versus axial disease, performance status 0 versus 1 to 3, prostate specific antigen less than 65 versus 65 ng/ml or greater and Gleason score less than 8 versus 8 or greater. As noted previously, E3805 stratified patients prospectively into low-volume and high-volume disease with "high-volume" defined for that protocol as the presence of visceral disease or four or more bony lesions including at least one bony lesion outside of the vertebral column and bony pelvis. Although a statistically significant difference in overall survival has not yet been reached in the subset of low volume patients receiving ADT plus chemotherapy versus ADT alone, the hazard ratio for death was remarkably similar in low volume patients at 0.63 as compared to 0.60 in the high-volume patients.(3) For purposes of this trial, we will not restrict chemotherapy to "high-volume disease" but will require the presence of imaging evidence of metastatic disease.

3.4 ANDROGEN DEPRIVATION THERAPY

Until the last decade, the most common means of obtaining castrate levels of testosterone in men with prostate cancer have been bilateral orchiectomy and administration of LHRH agonist therapy. Most men prefer to pursue medical castration, but LHRH agonists generally produce a testosterone spike before subsequent drop in testosterone values creating a need for lead-in therapy with an anti-androgen in men with high-volume disease where there is concern for potential "tumor flare." LHRH agonists do not generally produce castrate level testosterone until sometime between 15 and 28 days post-administration. (20). Newer direct LHRH antagonists such as degarelix (Firmagon®) do not produce a testosterone flare. In a randomized phase III study of 610 men with prostatic adenocarcinoma in varying disease states, patients were randomized to ADT with degarelix vs. leuprolide for a 12 month period. Suppression of testosterone to less than 0.5 ng/ml occurred at 3 days after a loading dose of 240 mg Degarelix in 96.1% of patients and no patients in the leuprolide group. (21). A subsequent extension trial was created where patients on leuprolide were re-randomized to two different degarelix doses. Analysis of data from this extension trial demonstrated that in patients with baseline PSA greater than 20 ng/ml, time for 25% of patients to achieve PSA failure (TTP25%) was significantly longer with degarelix than leuprolide at 407 versus 303 days; p=0.085.(22). LHRH antagonists thus represent an attractive option for rapid medical castration in a proposed cohort of patients with metastatic prostate cancer who will initially receive cytotoxic therapy without direct manipulation of the hormonal axis.

3.5 GENOMIC ANALYSIS IN METASTATIC PROSTATE CANCER

3.5.1 Tumor Heterogeneity in Prostate Cancer

As our ability to more quickly assess genomic changes in neoplastic tissue improves via next generation sequencing, the heterogeneity of genomic aberrations in advanced prostate cancer has been revealed. A variety of examinations of series of prostate cancer specimens have been performed all speaking to this heterogeneity.(23-25). A recent multi-institution protocol led by *Robinson et al.* conducted prospective whole exome and transcriptome sequencing from bone or soft tissue tumor specimens from a cohort of 150 men with mCRPC. 89% of examined patients had tumors with at least one clinically actionable genetic aberration including 62.7% of samples with alterations in the androgen receptor, 53.3% with mutations in TP53, and 49% with aberrations in the PI3K pathway. (26). Direct sequencing of tumor tissue is probably the most sensitive assay for genetic alterations but invasive. Several studies have looked at the role of analyzing circulating tumor DNA or cell free tumor DNA as an alternative less invasive technique for analyzing tumor genetic aberrations.(27, 28)

3.5.2 Guardant® Analysis

Guardant 360 is a commercial platform for digital sequencing of cell-free circulating tumor DNA (ctDNA) developed by Guardant Health®. The test is run on peripheral blood samples and analyzes circulating tumor DNA for 70 known cancer-related genes identifying missense mutations, amplifications, and a particular set of gene fusions. (29). In our own series of 79 patients with metastatic prostate cancer analyzed with this ctDNA platform and presented in recent abstract form, we detected genetic abnormalities in 92.5% of patients including 48% of patients with TP53 mutations, 47% with androgen

receptor alterations, and 19% with BRAF alterations. These were similar percentages to earlier data discussed based on a series of tumor biopsies.(26) We then retrospectively analyzed progression free survival during taxane chemotherapy (predominantly docetaxel) for 38 of the patients who had the taxane administered within one year of Guardant 360 analysis. Patients who had a TP53 genetic alteration detected on ctDNA analysis had improved PFS with taxane chemotherapy as compared to patients with wild-type TP53 (p= 0.032) while patients with PI3KCA missense mutations had decreased PFS with taxane chemotherapy as compared to patients with wild-type PI3KCA(p=0.0244).(30). This was not prospective data but suggests a role for incorporating genomic analysis of prostate cancer ctDNA in future clinical trials including this one looking at taxane-based therapy.

For our proposed trial, we will run Guardant assays, when feasible, on all patients at baseline. We will then see if baseline genomic signature can be correlated with responses to docetaxel alone and to the overall trial therapy. If possible, repeat Guardant assays could be run on patients as part of standard of care management after completion of trial therapy.

3.6 TRIAL RATIONALE AND HYPOTHESIS

As discussed in the above background, recent randomized trials have suggested an overall survival benefit to moving docetaxel therapy into the setting of hormone-sensitive metastatic prostate cancer. (3) While a statistically significant difference in survival in the E3805 trial in particular has at this point only been detected for patients with "high-volume disease," similar hazard ratios were present for lower volume disease, and it is very possible that a statistically significant survival difference will be detected as these patients are followed further. We hypothesize that an even greater survival benefit may be detected when administering docetaxel before androgen deprivation therapy in men with newly diagnosed metastatic disease. We hope to further this benefit by using a potentially superior means of androgen deprivation in degarelix. In this trial, we will evaluate PSA complete response at 10 months (7 months on ADT) among other efficacy endpoints as there are historical comparators for these endpoints and some precedent that they serve as surrogates for overall survival. (3, 31) See detailed explanation of endpoints starting in Section 3.8.

Our hypothesis that upfront docetaxel before ADT may improve outcomes is supported, as outlined above, by research in animal models and prostate cancer cell lines where prostate cancer death is increased when docetaxel is given in the non-castrate state.(15) Clinical data from the hormone receptor positive breast cancer setting also suggests a benefit to administering cytotoxic chemotherapy separately from manipulation of the hormonal access.(13) There appears to be greater hematologic toxicity from docetaxel when given in the recently castrated or non-castrate state as compared to with castrate level testosterone due to increased clearance of the drug in the castrate state, but this finding raises the question of whether greater exposure to the drug in the non-castrate state with G-CSF support might actually increase efficacy.(9) There have been studies primarily in the setting of biochemical recurrence proving the ability to give docetaxel without castration fairly safely without significant disease progression before ADT is ultimately initiated. (17) We hope to further

improve patient outcomes by employing a potentially better form of androgen deprivation therapy in degarelix. We will hopefully supplement the knowledge gained from this trial by exploring the genomic signature of ctDNA in subjects over the course of their therapy to gain insight into the serial changes that may occur and possibly correlate particular genetic aberrations with tumor response to early docetaxel chemotherapy and degarelix.

3.7 EXPLANATION OF PRIMARY ENDPOINT

The primary endpoint for this trial will be the percentage of patients at 10 months from start of trial therapy with undetectable PSA(less than or equal to 0.2 ng/ml). Using undetectable PSA as an endpoint is derived from earlier work suggesting this endpoint as prognostic of overall survival. *Hussain et al.* analyzed results from the SWOG/Intergroup-0612 trial which was a randomized phase III trial looking at continuous versus intermittent androgen deprivation in men with newly diagnosed metastatic prostate cancer after a lead-in of 7 months of ADT consisting of goserelin plus bicalutamide. Patients with PSA nadir less than 4 ng/ml were eligible for randomization, but the trial recorded the percentage of patients who achieved PSA nadir at 7 months less than or equal to 4 ng/ml and less than or equal to 0.2 ng/ml. Of 1395 enrolled patients who received induction ADT, 604 patients (43%) obtained a PSA nadir less than or equal to 0.2 ng/ml and maintained this at 7 months. Furthermore, an undetectable PSA (less than or equal to 0.2 ng/ml) at 7 months was a significant predictor of longer survival (HR 0.34; 95% CI 0.29-0.40; $p< 0.001$) as compared to not obtaining and maintaining such a value. The median overall survival was 13 months for 383 men with a PSA nadir of more than 4 ng/ml at the end of induction (95% CI, 11-16 months), 44 months for 360 men who had a PSA nadir of more than 0.2 ng/mL but 4.0 ng/mL or less at months 6 and 7 (95% CI, 39 to 55 months), and 75 months for 602 men with undetectable PSA ($\leq$ 0.2 ng/mL) at months 6 and 7 (95% CI, 62, 91 months).(31)

Subsequent SWOG trials including S0925 published in 2015 have used undetectable PSA, also defined as $\leq$ 0.2 ng/ml, at 7 months of ADT as a primary endpoint. SWOG 0925 randomized 210 patients with newly diagnosed metastatic prostate cancer to ADT (LHRH agonist plus bicalutamide) with or without the investigational agent cixutumumab. The trial did not detect a significantly different undetectable PSA rate between the two arms, but the control arm of 105 patients who received ADT alone provide another historical comparator with 34 patients (32.3%) having an undetectable PSA at 28 weeks.(32)

In an era of patients being treated with earlier chemotherapy, E3805, which as discussed earlier randomized men with newly diagnosed metastatic disease to ADT alone versus ADT plus 6 cycles of Docetaxel, did include as secondary endpoints the percentage of patients at 6 months and 12 months with undetectable PSA (less than 0.2 ng/ml). This trial, because of its initial design, likely contained higher volume patients than SWOG/Intergroup-0612, but the results of E3805 also suggest undetectable PSA at both 6 and 12 months as potential surrogates for overall survival. At 6 months, rate of undetectable PSA was 19.6% with ADT alone and 32% with ADT plus docetaxel ($p<0.001$). At 12 months, the rate was 16.8% in the ADT arm and 27.7% in the ADT plus docetaxel arm ($p<0.001$)(3).

It is difficult to find a historical time point for looking at undetectable PSA rate that is directly comparable to our trial since our treatment design is novel with chemotherapy

initially given independently from ADT. We have elected to have percentage of patients with undetectable PSA (less than or equal to 0.2 ng/ml) after 10 months on all therapy (7 months on ADT) as the primary endpoint. This endpoint could be compared to the "undetectable PSA rate at 6 months" on CHAARTED/E3805 since the "6 months" time point for the CHAARTED trial was calculated from time of randomization but the majority of patients were on ADT before randomization for an average of 1.2 months.(3) Thus the "6 month undetectable PSA rate" for the average patient on E3805 represented the effect of 7.2 months of ADT. The PSA at 10 months on all therapy (7 months on ADT) endpoint for our proposed trial would also be comparable to the SWOG/Intergroup-0612 undetectable PSA rate at 7 months of ADT exposure.(31).

3.8 EXPLANATION OF SELECT SECONDARY ENDPOINTS

3.8.1 Six-Month Undetectable PSA Rate

We propose evaluating patients on this trial for the secondary endpoint of proportion of men with newly diagnosed metastatic hormone sensitive prostate cancer who obtain and maintain a PSA complete response (less than or equal to 0.2 ng/ml) at 6 months after initiation of trial therapy. Although our trial design means that this endpoint will only represent 12 weeks on ADT, we speculate that the earlier docetaxel and more rapid castration with Degarelix as compared to LHRH agonists will yield an improvement in undetectable PSA rate even with this more limited ADT exposure as compared to the "6 month" time point on E3805.

4 SUBJECT SELECTION

4.1 INCLUSION CRITERIA

Patients eligible for study participation must meet all of the following criteria.

1. Histological or cytological diagnosis of adenocarcinoma of the prostate.

2. Metastatic disease identified via radiographic assessment by CT scans of the chest, abdomen, pelvis, and nuclear bone scan. MRI may be used if deemed necessary by the investigator. The CT portion of PET-CT can be used for inclusion in place of dedicated CT chest, abdomen, and pelvis as long as any non-bony lesions of concern are felt by the investigator to be adequately assessed with this imaging. Subsequent imaging on protocol should be with dedicated CT chest, abdomen, pelvis unless there are convincing rationale for repeat PET-CT (a bone scan is still required). See Section 8.5 for more details about radiographic assessment requirements.

   More specifically, patients must have at least one of the following at time of study enrollment:

   a) Any visceral metastases identified by CT scans,MRI or PET-CT.
   b) Site(s) of bony metastasis identified by nuclear bone scan, MRI, PET-CT and/or CT scan.

c) Lymph node based disease not considered to be within a single radiation therapy port (e.g. at or above the aortic bifurcation.)

3. Non-castrate testosterone level, >50 ng/dl, at study enrollment.

4. Age greater than or equal to 18 years.
5. ECOG performance status 0-2.

6. Meet the following hematologic criteria within 14 days of enrollment to trial:

   a) Absolute neutrophil count $\geq$ 1,500/mm^3
   b) Hemoglobin $\geq$ 8.0 g/dl (may be transfused)
   c) Platelet count $\geq$ 100,000 mm^3

7. Have adequate end-organ function as defined by the following parameters. All lab values must be obtained within 14 days of enrollment to trial:
   a) Creatinine clearance of $\geq$ 30 ml/min. Creatinine clearance should be determined by the Cockcroft-Gault formula (Appendix A)
   b) AST < 2 x institutional ULN
   c) ALT < 2 x institutional ULN
   d) Total bilirubin $\leq$ institutional ULN

8. Agree to use barrier methods of birth control during the docetaxel portion of the protocol and for at least one month after last docetaxel administration.

9. Informed and must sign and give written informed consent in accordance with institutional and federal guidelines.

4.2 EXCLUSION CRITERIA

Patients eligible for study participation CANNOT meet any of the following criteria:

1. CNS metastases (brain or leptomeningeal).

2. Osseous metastases felt in the opinion of the clinician to be high-risk for impending pathologic fracture or spinal cord compression.

3. Active cardiac disease defined as symptomatic congestive heart failure, history of NYHA Class III or IV Heart Failure, uncontrollable supraventricular arrhythmias, any history of a ventricular arrhythmia, active angina pectoris, myocardial infarction or coronary intervention within 6 months of registration.

4. Prior malignancy requiring systemic therapy within the last 5 years except for treated basal or squamous cell skin cancer. History of low-grade malignancies with limited potential to progress as determined by the primary investigator may be enrolled.

5. Subjects must not have received any previous androgen deprivation therapy (LHRH agonist or LHRH antagonist) or cytotoxic therapy for prostate cancer in the metastatic setting.

   Exception
   Patients may have received no more than 30 days of anti-androgen (e.g. bicalutamide) in the metastatic setting prior to the start of study treatment.

6. Subjects must not have had more than 36 months of hormonal therapy in combination with prostatectomy or radiation in the setting of localized disease and must not have shown any evidence of disease recurrence within 12 months after stopping hormonal therapy. Disease recurrence after hormonal therapy is defined as PSA > 0.2ng/dl after prostatectomy + hormonal therapy or PSA that is 2.0ng/dl more than the PSA nadir after radiotherapy + hormonal therapy. Previous hormonal therapy to the prostate must have stopped at least 12 months prior to enrollment.

7. Subjects must not have been treated with prior docetaxel in the setting of metastatic prostate cancer. Subjects may have been treated with docetaxel in the setting of localized prostate cancer (likely as a trial-based neoadjuvant or adjuvant approach to prostatectomy or radiation.) Subjects treated with this approach must not have shown any evidence of disease recurrence within 12 months after stopping docetaxel. Disease recurrence after docetaxel is defined as PSA > 0.2ng/dl after prostatectomy + docetaxel or PSA that is 2.0ng/dl more than the PSA nadir after radiotherapy +docetaxel. Previous docetaxel in the setting of localized prostate cancer must have stopped at least 12 months prior to study enrollment.

8. Palliative radiation therapy may have been received but not within the 30 days prior to study treatment.

9. Presence of peripheral neuropathy > Grade 1.

10. Known HIV-positive

11. Presence of any severe or uncontrolled concurrent medical condition felt in the opinion of the investigator to increase the risk of serious toxicity from the study therapy.

12. Prior hypersensitivity to any of the components of the study drugs.

4.3 INCLUSION OF WOMEN AND MINORITIES

Men of all races and ethnic groups are eligible for this trial.

4.4 SUBJECT REGISTRATION

The SIS Unit will provide patient registration services for the study. The SIS Unit will conduct a patient eligibility audit review of all eligibility source documents prior to patient

registration. These procedures are outlined in the CTO # 102509 Operations Manual. After obtaining signed informed consent and completion of required baseline assessments, eligible subjects will be registered upon the SIS Unit's verification of study eligibility. A unique subject number will be assigned to each patient. The SIS Unit will issue a registration confirmation email to the enrolling study team at the time of registration. This confirmation will include the patient's assigned study number. Subjects may not begin study drug until after this confirmation is issued.

5 STUDY INTERVENTION

5.1 AGENT ADMINISTRATION

5.1.1 Docetaxel

Patients will receive docetaxel 75 mg/m2 intravenously over 60 minutes (+/- 15 minutes) every 21 days for six cycles. The first four cycles of docetaxel will be without concurrent hormonal therapy of any kind. The last two cycles will be after initiation of degarelix (Firmagon®). Dose modifications for docetaxel are outlined in Section 6.

5.1.2 Degarelix

ADT for this trial will be with the direct LHRH antagonist degarelix (Firmagon®). Degarelix will be administered per the product label.

Degarelix will be administered for the first time on Day 1 +/- 2 days of cycle 5 of docetaxel. The first dose will be the standard loading dose of 240 mg SubQ. The drug is given as a deep subcutaneous injection into the abdominal region per product label.

The second dose will be 28 days later on Day 8 of cycle 6 of docetaxel. The second and subsequent doses of degarelix will be given at 80 mg SubQ q 28 days. Degarelix will be continued for the first 28 weeks of ADT (40 weeks of total trial therapy). At that point, the subject may continue degarelix or switch to LHRH agonist versus orchiectomy according to investigator/patient preference.

5.1.3 Regimen Description

REGIMEN DESCRIPTION

Agent	Dose	Route	Schedule
Docetaxel	75 mg/m2	IV over 60 minutes[a]	Day 1 of Cycle 1 – Cycle 6[b]
Degarelix	**Dose 1:** 240mg **Dose 2:** 80 mg **Subsequent Doses:** 80 mg	SubQ[c]	**Dose 1:** Cycle 5 Day 1 **Dose 2:** Cycle 6 Day 8 **Subsequent Doses:** Q 28 Days until 10 months(40 weeks) of trial therapy is completed

a. +/- 15 minutes
b. Cycle is 21 days
c. Degarelix should be administered as a SubQ injection in the abdomen.

5.2 PRE- AND POST- MEDICATIONS

5.2.1 Pre-Medications for Docetaxel

Patients will receive standard pre-medication prior to docetaxel to help prevent anaphylactic reaction and help mitigate later swelling. The premedications listed in this section are recommended, but may be modified per institutional guidelines and investigator discretion:

- Dexamethasone, 8mg PO twice daily the day before, day of, and day after docetaxel or 20 mg IV prior to docetaxel infusion
- Ondansetron 8 mg IV is recommended prior to docetaxel infusion
- Famotidine 20 mg IV is recommended prior to docetaxel infusion.
- Benadryl may be given at investigator discretion.

5.2.2 Post-Chemotherapy G-CSF

Patients will receive prophylactic GCSF with each cycle of docetaxel. This G-CSF may be given as pegfilgastrim(Neulasta®) 6 mg SubQ 24-72 hours after each dose of docetaxel, filgastrim(Neupogen ®) 5 mcg/kg/day SubQ on days 5-10 of each cycle, or as per institutional/investigator preference. G-CSF may be omitted if a patient has a history of reaction or develops anaphylactic reaction to the drug. G-CSF may also be omitted per investigator discretion or if a patient experiences side effects (bone pain, dyspnea, etc.) which in the best judgement of the investigator are attributable to the GCSF and not easily manageable

6 DOSE MODIFICATIONS

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

Subjects must have ANC $\geq$ 1,500/mm^3 and platelet count $\geq$ 100,000/mm^{3}on day of therapy to be treated with docetaxel. If a dose reduction is made, this reduced dose will be maintained for all subsequent cycles (no dose re-escalation). If a planned docetaxel dose must be delayed for three consecutive weeks, docetaxel will be discontinued and degarelix initiated immediately (and given every 28 days thereafter) or continued without docetaxel.

6.1 DOCETAXEL

6.1.1 Docetaxel Dose Levels

A subject may only have two dose reductions over the course of study drug administration. A need for a third dose reduction will require discontinuation of docetaxel and immediate initiation of degarelix (and given every 28 days thereafter) or continuation of degarelix without docetaxel.

Dose levels of docetaxel for this trial are as follows:

Dose Level	Docetaxel (mg/m2)

Level 0	75 mg/m2
Level -1	65 mg/m2
Level -2	55 mg/m2

6.1.2 Hematologic Toxicity

Dose adjustments on Day 1 of each cycle for myelosuppression should be made according to the following algorithm.

Event	**Docetaxel Dose**
Granulocyte decreased	
≥ 1,500/mm3	No change
1,000/mm3-1,499/mm3	Reduce one dose level and treat at investigator discretion. May also delay one week and reduce one dose level.
< 1000/mm3	Delay until recovery of neutrophil counts to ≥ 1,500/mm3 and reduce one dose level.
afebrile Neutropenia G4 for ≥ 7 days[a] Or Neutropenia G3 with fever[b] ≥ G3[b]	Delay until recovery of neutrophil counts to ≥ 1,500/mm3 and reduce one dose level. Any active infection must have been actively treated and clinically resolved before restarting docetaxel.
Thrombocytopenia	
≥ 100,000/mm3	No Change
75,000-99,000	Reduce one dose level and treat at investigator discretion. May also delay one week and reduce one dose level.
≤ 74,999	Delay dosing by one week then reduce by one dose level upon recovery of platelet counts to ≥ 100,000

a. ANC < 500/mm3
b. Single temperature > 38.3°C or three oral temperatures > 38.0°C in a 24-hour period.

6.1.3 Hepatic Dysfunction/Toxicity

ALT and bilirubin will be examined pre-study and prior to Day 1 of cycles 1-6 of docetaxel chemotherapy. Eligibility criteria in terms of hepatic studies are as defined in Section 4.1. Patients who develop hepatic dysfunction during docetaxel therapy will have the docetaxel adjusted according to the following algorithm:

Bilirubin		**ALT**	**Docetaxel Dose**
> ULN	or	> 5 x ULN	Delay dosing one week and then re-check. If Bilirubin recovers to < ULN AND AST < 3 x ULN, reduce docetaxel by one dose level and treat. If patient does not meet treatment criteria at 3 week delay, discontinue docetaxel and start Degarelix.
≤ ULN	and	>3 x ULN but ≤ 5 ULN	Reduce docetaxel by one dose level and treat.

A patient may only have two dose reductions over the course of therapy. A need for a third dose reduction will require discontinuation of docetaxel and immediate initiation of degarelix every 28 days.

6.1.4 Hypersensitivity Reactions for Docetaxel

Subjects should be monitored closely during all infusions of docetaxel to monitor for hypersensitivity reaction presenting as generalized rash, hypotension, bronchospasm, or severe anaphylaxis. Subjects should be pre-medicated to help prevent hypersensitivity reactions as in 5.2.1. Flushing or localized rash during infusion may be treated with Benadryl without stopping the docetaxel infusion. Any hemodynamic instability should prompt immediate stoppage of docetaxel and aggressive supportive care.
Subjects with Grade 4 hypersensitivity (life threatening reaction requiring pressors or ventilator support) should never be re-challenged with docetaxel. Subjects with episodes of Grade 3 hypersensitivity (prolonged reaction not initially responsive to stopping the infusion/supportive meds but not requiring pressors/ventilator support) can be re-challenged at a later date if agreed upon by the subject and investigator. Subjects with two Grade 3 hypersensitivity reactions should not be re-challenged with docetaxel.

6.1.5 Peripheral Neuropathy

Neuropathy	**Docetaxel Dose**
≥ Grade 3 Neuropathy (severe symptoms limiting self-care ADL's)	Discontinue docetaxel
Grade 2 Neuropathy (moderate symptoms limiting instrumental ADL's)	Hold docetaxel until resolves to ≤ Grade 1. At that point, reduce one dose level and treat. If not recovered to ≤ Grade 1 at 3 weeks, discontinue docetaxel.

6.1.6 Other Docetaxel Related Toxicities

Subjects with other toxicities thought to be docetaxel-related that are ≤ Grade 2 may be managed supportively and treated on schedule without dose reductions.

Subjects who develop other toxicities that are ≥ Grade 3 and thought to be docetaxel-related should have docetaxel held until toxicity resolved to ≤ Grade 1. At that point, docetaxel may be re-instituted at investigator discretion with a one level dose-reduction. A patient may only have two dose reductions over the course of therapy. A need for a third dose reduction will require discontinuation of docetaxel and immediate initiation of ADT.

6.1.7 Investigator Concern for Clinical Progression

PSA progression on docetaxel will not firmly be established as a measurable endpoint until after 4 cycles of docetaxel as in Section 10.2.2. It is the right of the investigator to determine that radiographic or clinical progression has occurred at any point during therapy or that docetaxel without ADT is no longer in the best interest of the patient for any reason at any point during the first four cycles of docetaxel. If a decision is made that docetaxel without ADT is no longer in the best interest of the patient, the patient may be immediately administered loading dose (dose#1) of degarelix and remain on trial. An

attempt should be made to obtain repeat imaging (CT scans and a bone scan) as would have been done after the 4 cycles of upfront docetaxel, but obtaining this imaging does not need to hold up initiation of ADT. The decision as to whether to continue a total of 6 doses of docetaxel will be between the investigator and the patient, but in either case the patient may remain on the trial. Any subsequent docetaxel cycles would be administered at dosing as per protocol. Subsequent degarelix injections would be q 28 days as per protocol.

6.2 DEGARELIX

6.2.1 Hypersensitivity

If a subject develops a significant hypersensitivity reaction to degarelix (anaphylaxis), the drug should be discontinued and the subject should not be re-challenged with degarelix. A subject who has had degarelix discontinued for hypersensitivity reaction should be switched four weeks later to alternative LHRH agonist or bilateral orchiectomy per investigator/patient discretion.

6.2.2 Cutaneous Site Reactions

Temporary erythema and pain at the injection site are common with degarelix. Attempts to minimize site reactions should be made by rotating injection sites in the abdomen and avoiding sites under constant pressure such as at the beltline. Patients who develop Grade 1 or 2 Injection Site Reactions (ISR's) can be retreated with Degarelix at the standard dosing and interval. Patients who develop Grade 3 ISR's should not receive any additional degarelix and should subsequently be switched to LHRH agonist or undergo orchiectomy per patient/investigator preference.

6.2.3 Monitoring Testosterone Level

Subjects will have their serum testosterone level monitored serially during therapy. Subjects will have their serum testosterone level drawn at Point A (screening), Point B (before the first dose of degarelix), Point C (before their second dose of degarelix), and then every twelve weeks. Interventions for non-castrate levels of testosterone will be as follows:

Time Point	Testosterone Level	Intervention
Point C (before second dose of degarelix)	> 100 ng/dl or > 50 ng/dl and less than 50% decline from Point B(pre-degarelix)	Re-load the patient with 240 mg SC x1 and then recheck testosterone level in four weeks.
Four weeks after a degarelix re-load	> 50 ng/dl	Discontinue degarelix and switch to alternative LHRH agonist or bilateral orchiectomy per investigator/patient discretion.
Any subsequent testosterone check	> 50 ng/dl	Re-load the patient with 240 mg SC x1 and then recheck testosterone level in four weeks.
Any subsequent testosterone check	$\leq$ 50 ng/dl	Continue degarelix 80 mg SC every 4 weeks.

7 CONCOMITANT THERAPY

7.1 PERMITTED MEDICATIONS – USE WITH CAUTION

Docetaxel is a substrate and moderate inhibitor of CYP3A4. Concomitant drugs that are strong CYP3A4 inhibitors should be used with caution.

7.2 PROHIBITED MEDICATIONS

Anti-androgens (e.g. bicalutamide) may have been used for no more than 30 days before trial enrollment. At enrollment, all anti-androgens must be stopped. LHRH-agonists or LHRH-antagonists may not have been administered in the metastatic setting as outlined in Section 4.2 (bullet point 3). LHRH agonists/agonists are only allowed on this trial as outlined in Section 4.2 (bullet point 3).

8 STUDY ASSESSMENTS

8.1 GENERAL CONSIDERATIONS

- Screening and baseline evaluations will be performed within 14 days of study enrollment.
- Screening radiologic assessments will take place within 28 days of study enrollment.
- Physical exam and laboratory testing will be conducted prior to drug administration on days when drug is administered. Safety labs can be drawn up to 3 days prior to scheduled dose.
- Study drug may be administered +/- 3 days. If holidays or inclement weather cause a greater than +/- 3 day delay, this will not be considered a protocol deviation.

8.2 HISTORY AND PHYSICAL

History and physical exam, including ECOG performance status should be performed at baseline and prior to drug administration. The physical exam should include at least vital signs, height, weight, evaluation of cardiovascular system, lungs, abdomen, extremities, neurologic system to include assessment of any baseline peripheral neuropathy, and skin. Height will be collected prior to day 1 drug administration.

8.3 CONCOMITANT MEDICATIONS

Concomitant medications will be reported at baseline and each subsequent clinic evaluation.

8.4 LABORATORY ASSESSMENTS

8.4.1 Safety Labs

CBC-Diff and CMP (complete metabolic profile) will be conducted at baseline and prior to each drug administration. A CMP includes sodium, potassium, creatinine, total bilirubin, AST, ALT, Alkaline phosphatase, calcium and albumin.

Testosterone level will be assessed at baseline and followed as in Section 6.2.3. (C6D8 testosterone can be done at a non-MUSC facility if necessary - MUSC lab is preferred)

8.4.2 PSA

PSA will be drawn at baseline, before each dose of docetaxel (Day 1 of each cycle before drug administration), on Cycle 4 Day 8 of docetaxel (C4D8 PSA can be done at a non-MUSC facility if necessary - MUSC lab is preferred), before each monthly dose of degarelix, and at end of study.

8.4.3 Cell-Free Circulating Tumor DNA analysis

Whole blood samples will be drawn for Guardant360® cell-free circulating tumor DNA analysis upon enrollment to the trial before study drug administration.

8.5 RADIOGRAPHIC ASSESSMENTS

Subjects will have screening nuclear bone scan (Technetium-99) and CT imaging of the chest, abdomen, and pelvis (with or without contrast per investigator discretion). CT, PET-CT and/or MRI may be done within 28 days prior to enrollment. The bone scan may be completed no more than 56 days before study enrollment. MRI may take the place of CT scan if deemed necessary by the investigator, but every attempt should be made to keep the modality of follow-up imaging consistent throughout the study. The CT portion of PET-CT can be used for inclusion/screening in place of dedicated CT chest, abdomen, and pelvis as long as any non-bony lesions of concern are felt by the investigator to be adequately assessed with this imaging. Subsequent imaging on protocol should be with dedicated CT chest, abdomen, pelvis unless there are convincing rationale for repeat PET-CT (a bone scan is still required).

Subjects will have repeat nuclear bone scan and CT imaging of the chest, abdomen, and pelvis (or MRI) after 4 cycles of docetaxel (between cycle 4 Day 8 and Cycle 5 day 1 before degarelix). An attempt should be made to repeat radiographic imaging after any upfront docetaxel if the decision is made to abort this approach early and initiate degeralix as in Section 6.1.7. These radiographic tests will also be repeated at the end of study or, if before 10 months, at time of PSA progression or time of concern for clinical progression as determined by the investigator. If a patient stops therapy for any reason during the degarelix-only portion of the trial, an attempt should be made to repeat the baseline radiographic imaging if deemed acceptable to the patient and treating physician.

8.6 STUDY CALENDAR[a]

	Screening [b]		C1 Day 1	C2 Day 1	C3 Day 1	C4 Day 1	C4 Day 8	C5 Day 1	C6 Day 1	C6 Day 8						End of Study	Follow Up (Q 3 months)[m]
								Deg. dose #1		Deg. dose #2	Deg. dose #3	Deg. dose #4	Deg. dose #5	Deg. dose #6	Deg. dose #7		
Day on Study			**1**	**22**	**43**	**64**	**71**	**85**	**106**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	
Test or Procedure[c]		REGISTRATION															
Informed Consent	X																
Physical Exam, ROS	X		X	X	X	X		X	X		X	X	X	X	X	X	X
ECOG Performance Status	X		X	X	X	X		X	X		X	X	X	X	X	X	X
Vital Signs[l], Weight	X		X	X	X	X		X	X		X	X	X	X	X	X	X
Concomitant Medications Assessment	X		X	X	X	X		X	X							X	X
CMP	X		X	X	X	X		X	X		X	X	X	X	X	X	X
CBCD	X		X	X	X	X		X	X		X	X	X	X	X	X	X
PSA	X[b]		X[b]	X	X	X	X[n]	X	X		X	X[g]	X	X	X	X	X
Serum Testosterone	X							X		X[n]			X			X[j]	X
AE Assessment			X	X	X	X		X	X		X	X	X	X	X	X	X
Radiographic Tumor Assessment[f]	X							X[e]								X[k]	
Follow Up																	X[h]
Study Drug Administration[c, d]																	
Docetaxel			X	X	X	X		X	X								
Degarelix								X		X	X	X	X	X	X		
Correlatives																	
Guardant Analysis			X[i]													X[i]	

a. Docetaxel cycle is 21 days. C=cycle; D=day; W=week

b. Screening and baseline evaluations to be performed within 14 days of study enrollment. Informed consent and CT/MRI/PET-CT will take place within 28 days of study enrollment (Note: the use of the CT portion of the PET-CT is only permissible for inclusion/screening as long as any non-bony lesions of concern are felt by the investigator to be adequately assessed with this imaging. Subsequent imaging on protocol should be with dedicated CT chest, abdomen, pelvis unless there are convincing rationale for repeat PET-CT. A bone scan is still required). Bone scan may be done within 56 days of study enrollment. Assessments completed within 3 days prior to Cycle 1 Day 1 do not need to be repeated. PSA collected within 7 days prior to cycle 1 day 1 does not need to be repeated.

c. Study drugs and study procedures may be completed +/- 3 Days. All labs must be completed before drug administration.

d. If docetaxel is held > 3 weeks (1 cycle), docetaxel will be permanently stopped and degarelix administration will begin or continue without docetaxel.

e. The radiologic response assessment to be completed **AFTER** Cycle 4 Day 8 but **BEFORE** the initiation of degarelix/docetaxel on Cycle 5 Day 1. If Docetaxel stopped because of toxicity before Cycle 5 Day 1, this imaging is to be completed before administration of degarelix. If decision made per investigator discretion to administer degarelix before finishing four cycles docetaxel, an attempt should be made to obtain repeat CT scans/bone scan but imaging does not need to hold up degarelix administration.

f. Radiographic assessments should also be repeated at PSA progression or at time of concern for clinical progression as determined by the investigator.
g. PSA at 24 weeks on study will analyzed as > 0.2 ng/ml or ≤ 0.2 ng/ml
h. ADT modality after 10 months (LHRH agonist vs. antagonist) would be per investigator/patient discretion but should be continued if clinically indicated. PSA, disease status and current therapy will be collected every three months for up to two years after the end of study visit.
i. See Section 13 for details. The post-study Guardant analysis is not required per the protocol, but if completed, results of the Guardant analysis will be included in the data set.
j. If radiographic disease progression is noted at end of study, serum testosterone should also be measured if not already done.
k. If patient comes off study prior to completion of study, scans should be repeated at the end of study visit as clinically indicated.
l. Vital signs include pulse, temperature, and blood pressure.
m. Follow up will be done every 3 months +/- 15 days.
n. C4D8 PSA and C6D8 testosterone can be done at a non-MUSC facility if necessary (MUSC lab is preferred)

8.7 CRITERIA FOR REMOVAL FROM PROTOCOL TREATMENT

Subjects may discontinue study treatment at any time. Any subject who discontinues treatment will be asked to return to the study center to undergo end of treatment assessments as outlined within Study Calendar (Section 8.6). The primary reason for discontinuation will be recorded. In the absence of treatment delays due to adverse events, study drug administration may continue for 10 months or until one of the following criteria applies:

- Radiographic disease progression
  - **NOTE**: If this occurs during the first 4 cycles of docetaxel or on imaging after 4 cycles before initiation of degarelix, the patient may start on degarelix per protocol if acceptable to the patient/investigator)
- Clinical disease progression
  - **NOTE:** If this occurs during the first 4 cycles of docetaxel or on imaging after 4 cycles before initiation of degarelix, the patient may start on degarelix per protocol if acceptable to the patient/investigator)
- Inter-current illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or require discontinuation of study drugs
- Completion of protocol treatment.
- Unacceptable toxicity
- Death
- Subject may withdraw from the study at any time for any reason.
- Concomitant treatment with a prohibited medication
- Subject non-compliance

8.8 DURATION OF FOLLOW UP

After the end of study, subjects will be followed as clinically indicated thereafter at least every 3 months for progression while continuing ADT. PSA, current therapy, and disease status will be recorded at these visits at least out 2 years post end of study therapy.

9 DRUG INFORMATION

9.1 DOCETAXEL

Docetaxel is available through commercial supply. To supplement the information below, please see product package insert for complete pharmacologic, stability, preparation and safety information.(33)

9.1.1 Description

Docetaxel (TAXOTERE ®), a semisynthetic analog of paclitaxel, is chemically described as (2R, 3S)-N-carboxy-3-phenylisoserine, N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.; Empirical formula, $C_{43}H_{53}NO_{14}$; Molecular weight: 861.9.

9.1.2 Pharmacology

Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules, leading to pre-mature mitosis and then apoptosis. Docetaxel has been evaluated in a variety of dosing schedules up to 100 mg/m2 every 3 weeks. Docetaxel is widely distributed in tissues with a linear relationship between dose and area under the plasma concentration-time curve. (34) Docetaxel is greater than 90% bound in plasma. Metabolism is primarily via the cytochrome p450 (CYP)3A4 system with biliary excretion into feces. The drug is less than 5% renally cleared.(35)

9.1.3 Mechanism of Action

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. (36)

9.1.4 Product Identification, Packaging and Labeling

Docetaxel for Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, diluent (13% ethanol in Water for Injection) vial. The following strengths are available: 80 mg and 20 mg.

9.1.5 Handling

Docetaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handing and preparing docetaxel solutions. The use of gloves is recommended. If docetaxel concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If docetaxel concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

9.1.6 Storage

Store between 2°C and 25°C (33°F and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

9.1.7 Preparation for Injection

Docetaxel for Injection Concentrate requires two dilutions prior to administration. Please follow the preparation instructions provided below. Note: Both the “Docetaxel for Injection Concentrate” and the diluent vials contain overfill.

Preparation of the initial diluted solution: Gather the appropriate number of vials of docetaxel for Injection Concentrate and diluent (13% Ethanol in Water). If the vials were refrigerated, allow them to stand at room temperature for approximately 5 minutes. Aseptically withdraw the contents of the appropriate diluent vial into a syringe and transfer it to the appropriate vial of docetaxel for Injection Concentrate. If the procedure is followed as described, an initial diluted solution of 10 mg docetaxel /ml will result.

Gently rotate the concentrate and diluent. The initial diluted docetaxel solution (10 mg docetaxel /ml) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipates prior to continuing the preparation process. The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

Preparation of the final dilution for infusion: Aseptically withdraw the required amount of initial diluted docetaxel solution (10 mg docetaxel/ml) with a calibrated syringe and inject into a 250 ml infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/ml. If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/ml docetaxel is not exceeded. Thoroughly mix the infusion by manual rotation. As with all parenteral products, docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel for Injection initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded. Contact of the docetaxel concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

9.1.8 Stability of Docetaxel

The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours. Docetaxel infusion, if stored between 2°C and 25°C (36°F and 77°F) is stable for 4 hours. Fully prepared docetaxel infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour IV administration).

9.1.9 Toxicity

The following events are expected in greater than 10% of patients: CNS toxicity, including neuropathy; alopecia; dermatological reaction; nail disease; fluid retention; stomatitis; diarrhea; nausea; vomitingneutropenia; leukopenia; anemia; thrombocytopenia; febrile neutropenia; increased serum transaminases; hypersensitivity; infection; weakness; myalgia; neuromuscular reaction; pulmonary reaction; and fever.

The following events are expected in 1-10% of patients: decreased left ventricular ejection fraction; hypotension; peripheral motor neuropathy; dysgeusia; increased serum bilirubin, increased serum alkaline phosphatase; infusion site reactions including hyperpigmentation, inflammation, redness, dryness, phlebitis, extravasation, and swelling of the vein; and arthralgia.

The following events are expected in <1% of patients or are the result of postmarketing and/or case reports: abdominal pain, acute myelocytic leukemia, acute respiratory distress, alopecia, anaphylactic shock, anorexia, ascites, atrial fibrillation, atrial flutter,

back pain, bronchospasm, cardiac arrhythmia, cardiac tamponade, chest pain, chest tightness, chills, colitis, confusion, conjunctivitis, constipation, cystoid macular edema, deep vein thrombosis, dehydration, duct obstruction, disseminated intravascular coagulation, drug fever, duodenal ulcer, dyspnea, ECG abnormality, epiphora, erythema multiforme, esophagitis, flushing, gastrointestinal hemorrhage, gastrointestinal obstruction, gastrointestinal perforation, hearing loss, hemorrhagic diathesis, hepatitis, hypertension, hyponatremia, intestinal obstruction, interstitial pulmonary disease, ischemic colitis, lacrimation, localized erythema of the extremities, loss of consciousness (transient), lymphedema (peripheral) multi-organ failure, myelodysplastic syndrome, myocardial infarction, neutropenic enterocolitis, ototoxicity, pain, palmar-plantar erythrodysesthesia, pneumonia, pneumonitis, pruritus, pulmonary edema, pulmonary embolism, pulmonary fibrosis, renal failure, renal insufficiency, respiratory failure, skin changes, seizure, sepsis, sinus tachycardia, skin rash, Stevens-Johnson syndrome, subacute cutaneous lupus erythematosus, syncope, tachycardia, thrombophlebitis, toxic epidermal necrolysis, unstable angina pectoris, visual disturbance.

9.1.10 Particular Toxicities of Note

9.1.10.1 Neutropenia

Neutropenia is commonly encountered with Docetaxel. Patients on this trial will receive prophylactic G-CSF but should still be monitored for neutropenia and associated infection.

9.1.10.2 Hypersensitivity

Steroid pre-medication is required as in Section 5.2.1. Severe hypersensitivity has been reported even with steroid medication and patients must be managed closely during infusion as in Section 6.1.4.

9.1.10.3 Neurologic Effects

Severe neurosensory changes with docetaxel including paresthesias, dysesthesia, and pain have been observed. Dose modifications for peripheral neuropathy should be made as in Section 6.1.5.

9.1.10.4 Fluid Retention

Severe fluid retention has been reported following docetaxel and is partially mitigated by steroid pre-medication. In a trial of 92 breast cancer patients pre-medicated with 3-day steroids, moderate fluid retention occurred in 27.2% of patients and severe retention in 6.5%. Patients who develop edema should be treated with supportive measures including salt restriction and/or diuretics as per investigator discretion.

Adverse events associated with the use of docetaxel in the TAX327 trial are shown in Appendix B.

9.2 DEGARELIX (FIRMAGON®)

Degarelix will be provided by Ferring USA.

9.2.1 Description

Degarelix (Firmagon®) is a synthetic linear decapeptide containing seven unnatural amino acids. The chemical name is D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-4-[[[(4S)-hexahydro-2,6-dioxo-4-pyrimidinyl]carbonyl]amino]-L phenylalanyl-4-[(aminocarbonyl)amino]-D-phenylalanyl-L leucyl-N6-1-methylethyl)-L-lysyl-L-prolyl. Empirical formula is $C_{82}H_{103}N_{18}O_{16}Cl$ with a molecular weight of 1632.3 Da. Firmagon® comes as a sterile lyophilized powder for injection containing degarelix as the acetate and mannitol.

9.2.2 Mechanism of Action

Degarelix is a GnRH receptor antagonist. It binds reversibly to the pituitary GnRH receptors, thereby reducing the release of gonadotrophins and consequently testosterone.

9.2.3 Packaging

Degarelix is available as:

Starting dose – one carton contains:

- Two vials each with 120 mg powder for injection
- Two prefilled syringes containing 3 mL of sterile water for injection, USP
- Two vial adapters
- Two administration needles

Maintenance dose – one carton contains:

- One vial with 80 mg powder for injection
- One prefilled syringe containing 4.2 mL of sterile water for injection, USP
- One vial adapter
- One administration needle

9.2.4 Handling

Discard all components safely in an appropriate biohazard container.

9.2.5 Storage

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). Reconstituted drug must be administered within one hour after addition of sterile water for injection.

9.2.6 Administration

Degarelix is administered as a subcutaneous injection in the abdominal region only. The drug is supplied as a powder to be reconstituted with Sterile Water for Injection. Package insert/diagram for administration must be read prior to drug administration.

<u>For starting dose:</u>
One starting dose comprises 240 mg given as two 3 mL injections of 120 mg each.
Powder for injection 120 mg:

One vial of FIRMAGON 120 mg contains 120 mg degarelix. Each vial is to be reconstituted with a prefilled syringe containing 3 mL of Sterile Water for Injection. 3 mL is withdrawn to deliver 120 mg degarelix at a concentration of 40 mg/mL.

For maintenance doses:
One maintenance dose comprises 80 mg given as one 4 mL injection.
Powder for injection 80 mg:
One vial of FIRMAGON 80 mg contains 80 mg degarelix. Each vial is to be reconstituted with a prefilled syringe containing 4.2 mL of Sterile Water for Injection. 4 mL is withdrawn to deliver 80 mg degarelix at a concentration of 20 mg/mL.

9.2.7 Toxicity

The following events are expected in greater than 10% of patients: Fatigue, hot flashes, increased GGT, weight loss, weight gain, increased serum transaminases, and fever. Injection site reactions including pain, erythema, swelling, induration, nodules and infections were also seen in greater than 10% of patients.

The following events are expected in 1%-10% of patients: hypertension, chills, dizziness, headache, insomnia, diaphoresis, hypercholesterolemia, gynecomastia, constipation, nausea, diarrhea, UTI, erectile dysfunction, testicular atrophy, increased ALT and AST, antibody development, back pain, arthralgia, weakness and night sweats.

9.2.8 Particular Toxicities of Note

9.2.8.1 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, urticaria, and angioedema have been noted post-marketing of Degarelix. If this occurs during injection, stop immediately and manage supportively. If hypersensitivity occurs, subsequent ADT should be as in Section 6.2.1.

9.2.8.2 QT Prolongation

Androgen deprivation therapy may prolong the QT/QTC interval. Although prolonged QT interval is not an exclusion for this trial, investigators should consider periodic monitoring of ECG in patients with congenital long QT syndrome or known ventricular dysrhythmia.

10 MEASURES OF EFFECT

10.1 DEFINITIONS:

- **Evaluable for objective response:** Only those subjects who have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according

to the definitions in Sections 10.2 and 10.3 (Note: Subjects who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Subjects must have at least one measurable lesion to qualify for radiographic response analysis. Subjects do not have to have measurable disease to enroll to the study.

- **Evaluable for toxicity**: All subjects will be evaluable for toxicity from the time of first dose of study drug until the end of study visit. Toxicity assessment will be based on NCI CTCAE v. 4.0. AEs and SAEs will be reported as outlined in Section 14.

10.2 PSA EVALUATION AND RESPONSE CRITERIA

10.2.1 Methods for Evaluation of PSA Response

Serum PSA will be obtained at baseline and then before each dose of docetaxel. PSA will also be drawn on Cycle 4 Day 8 of docetaxel to help facilitate calculation of PSA response to chemotherapy. Once docetaxel has been completed or stopped, PSA will be obtained every four weeks before each dose of degarelix. After 10 months, PSA will be measured every 3 months.

Because there are no defined criteria for PSA progression before initiation of ADT, we will employ the following criteria modified from Prostate Cancer Working Group Criteria.(37)

10.2.2 PSA Response Criteria during Docetaxel Chemotherapy:

PSA Response Criteria will be defined as:

- **PSA Complete Response:** PSA level less than or equal to 0.2 ng/ml for two consecutive measurements at least two weeks apart. Date of complete response will be defined as the date of first recorded value less than 0.2 ng/ml.

- **PSA Partial Response:** Decline of PSA from trial baseline of > 50% for two consecutive measurements at least two weeks apart. Date of partial response will be defined as the date of first recorded decline of > 50% baseline.

- **PSA Progression:** PSA progression will be defined as > 25% increase from the PSA nadir (lowest PSA value recorded since trial enrollment) and ≥ 2 ng/dl above the nadir. Two consecutive increases must be recorded at least two weeks apart. Date of PSA progression will be defined as the first recorded PSA value that is a > 25% increase from the PSA nadir and > 2 ng/dl above the nadir. PSA progression will not be established during the first 12 weeks of therapy (4 cycles of docetaxel) as defined by PCWG2 criteria. Thus subjects with no PSA decline from baseline during therapy will have date of PSA progression defined as first PSA value after 12 weeks that is a > 25% increase from the PSA nadir and > 2 ng/dl above the nadir. Patients whose PSA level meets the criteria for progression on Cycle 4 Day 8 and Cycle 5 Day

1(before ADT) will be defined as having had progressive disease during the docetaxel only portion of the trial.

10.2.3 PSA Response/Progression Criteria After ADT Initiated

PSA Response Criteria after ADT Initiated will be defined as:

- **PSA Complete Response:** PSA level less than or equal to 0.2 ng/ml for two consecutive measurements at least three weeks apart. Date of complete response will be defined as the date of first recorded value less than 0.2 ng/ml.

- **PSA Partial Response:** Decline of PSA from trial baseline of > 50% for two consecutive measurements at least three weeks apart. Date of partial response will be defined as the date of first recorded decline of > 50% baseline.

- **PSA Progression:** PSA progression will be defined as > 25% increase from the PSA nadir (lowest PSA value recorded since trial enrollment) and ≥ 2 ng/dl above the nadir. Two consecutive increases must be recorded at least three weeks apart. Date of PSA progression will be defined as the first recorded PSA value that is a > 25% increase from the PSA nadir and > 2 ng/dl above the nadir. PSA progression will not be established during the first 12 weeks of therapy (4 cycles of docetaxel) as defined by PCWG2 criteria. Thus subjects with no PSA decline from baseline during therapy will have date of PSA progression defined as first PSA value after 12 weeks that is a > 25% increase from the PSA nadir and > 2 ng/dl above the nadir.

10.3 RADIOGRAPHIC EVALUATION AND RESPONSE CRITERIA

Radiographic Response will be determined by RECIST 1.1 Response Criteria. Baseline tumor burden of measurable and non-measurable disease will be measured and then compared on subsequent imaging. See RECIST criteria in Section 10.3.3.

10.3.1 Methods for Evaluation of Radiographic Response

Subjects will have a nuclear bone scan and CT imaging of the chest, abdomen and pelvis as outlined in Section 8.5. Scans will be completed at baseline and repeated after 4 cycles of docetaxel, prior to the initiation of degarelix. Radiographic assessment should also be repeated at PSA progression or at time of concern for clinical progression, as determined by the investigator.

10.3.2 Disease Parameters

Measurable non-lymphatic disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >10 mm with CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the lesion has been radiated in the metastatic setting, it will not count as measurable disease. If the patient has disease recurrence after previous

definitive radiation to the prostate/pelvis and new disease in the previously radiated field, this tumor can count as measurable disease.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT 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/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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 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, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up if the information is available.

10.3.3 Radiographic Response Criteria

The evaluation of target lesions will be based on the RECIST 1.1 criteria as summarized in the table below.

Complete Response (CR):	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.
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

The evaluation of non-target lesions will be based on the RECIST 1.1 criteria as summarized in the table below.

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. 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).
Progressive Disease (PD):	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

10.4 SYMPTOMATIC DETERIORATION

Subjects with global deterioration of health requiring discontinuation of all therapy will be classified as having symptomatic deterioration.

10.5 PROGRESSION-FREE SURVIAL

PFS is defined as the duration of time from start of treatment to time of disease progression or death, whichever comes first.

10.6 OVERALL SURVIVAL

Overall survival is defined as the time interval from trial enrollment to death due to any cause. Survival times will be censored for patients lost to follow-up or still alive at the trial's termination.

11 DEFINITION OF ENDPOINTS

11.1 PRIMARY ENDPOINT

11.1.1 Undetectable PSA at 10 months

The Primary endpoint for this trial is a binary indicator of PSA less than or equal to 0.2 ng/dl at 10 months (40 weeks) on study. This also represents 7 months (28 weeks) on androgen deprivation therapy with degarelix.

11.2 SECONDARY ENDPOINTS

11.2.1 Undetectable PSA at 6 months.

Undetectable PSA at 6 months is a binary indicator for each patient of PSA less than or equal to 0.2 ng/dl at 6 months (24 weeks) on study. This also represents 3 months (12 weeks) on androgen deprivation therapy with degarelix.

11.2.2 Toxicity

Toxicity for all evaluable patients will be defined by CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0.

11.2.3 Disease Progression During First four cycles of Docetaxel

Disease Progression during the first four cycles of Docetaxel will be defined as any manner of disease progression that occurs before degarelix is administered, either after four cycles of docetaxel or if stoppage of docetaxel is required before four cycles administered. Specifically, disease progression during docetaxel will include any subject who meets criteria for:

a) PSA Progression during Docetaxel: This will be defined as in Section 10.2.2. PSA progression will not be defined until after 4 cycles of docetaxel are administered (Cycle 5 day 1 before degarelix administration) unless clinical progression(symptomatic deterioration), radiographic progression, toxicity, or investigator/patient discretion requires stoppage of docetaxel before four cycles administered. For example, if a subject's docetaxel is discontinued after two cycles because of toxicity, and PSA before what would have been cycle 3 meets criteria for PSA progression, this will be defined as PSA and disease progression during docetaxel.

b) Radiographic Progression during Docetaxel: This will be defined by RECIST 1.1 criteria as in Section 10.3.3. Re-imaging will take place after four cycles docetaxel or at time that docetaxel is stopped if clinical progression(symptomatic deterioration), toxicity, or investigator/patient discretion requires stoppage of docetaxel before four cycles administered. For example, if a subject's docetaxel is discontinued after two cycles because of toxicity, radiographic imaging will be repeated at that point. If the new images meet criteria for radiographic progression, this will be defined as radiographic and disease progression during docetaxel.

c) Symptomatic Deterioration – If investigator discretion is that the patient is clinically deteriorating because of progressive disease, docetaxel will be stopped and ADT started. This will be defined as clinical/disease progression but effort should be made to ensure that the clinical deterioration is in fact from progressive neoplastic disease and not treatment-related toxicity or other separate medical event.

11.2.4 PSA Response uring Docetaxel

The frequency of PSA response during docetaxel will be determined after four cycles of docetaxel (Cycle 4 Day 8 and Cycle 5 Day 1 before degarelix). The definitions of partial and complete PSA response will be defined as in Section 10.2.2. If clinical progression

(symptomatic deterioration), radiographic progression, toxicity, or investigator/patient discretion requires stoppage of docetaxel before four cycles administered, PSA at time of docetaxel stoppage can be evaluable for response.

11.2.5 Time to Development of Castration Resistance

This will be defined as the time from initial Degarelix injection to the time of disease progression (clinical, radiographic (as in Section 10.3.3), or PSA as in Section 10.2.3). Determination of castration resistant disease status will require disease progression and a measured serum testosterone level less than 50 ng/dl. Thus, if disease progression is noted, serum testosterone level should be measured if not already done so.

11.2.6 Progression Free Survival

Progression free Survival (PFS) will be defined as the duration of time from start of study treatment to time of disease progression or death, whichever comes first.

11.2.7 Overall Survival

OS is defined as the time interval from trial enrollment to death due to any cause. Survival times will be censored for patients lost to follow-up or still alive at the trial's termination.

11.3 TERTIARY/EXPLORATORY ENDPOINTS

See Section 13 - "Correlative Studies."

12 STATISTICAL CONSIDERATIONS AND DETERMINATION OF SAMPLE SIZE

12.1 STUDY DESIGN OVERVIEW

This will be a single-arm non-blinded interventional Phase II study enrolling a maximum of 50 patients at up to 4 sites. The primary endpoint is PSA less than or equal to versus greater than 0.2 ng/ml at 10 months after initiation of treatment.

Patients will be considered evaluable for efficacy if they complete at least one cycle of docetaxel Any patient who receives study therapy will be evaluable for toxicity. Patients who discontinue treatment will still be followed for clinical outcomes. Only patients who leave the study and are lost to follow-up, or leave the study and do not agree to have their clinical data included in the study would be considered inevaluable and replaced.

12.2 STATISTICAL JUSTIFICATION OF SAMPLE SIZE FOR PRIMARY OBJECTIVE

The sample size of 50 is based on undetectable PSA (i.e., PSA $\leq$0.2 ng/mL) at 10 months (7 months on ADT). Our null hypothesis is based on an assumed rate of undetectable PSA of 32% (CHAARTED/E3805 "6 month" PSA rate for the chemotherapy plus ADT arm as discussed in Section 3.8).(3) We hypothesize that our study treatment approach has a 50% rate of undetectable PSA at 10 months. With 50 patients, we have 83.9% power to detect this difference based on a one-sided alpha of 0.0503 based on a Fisher's exact binomial test. That is, if the one-sided alpha level is less than 0.0503, we will reject the null hypothesis. If we observe 22 or more patients with undetectable PSA at 10 months out of 50 patients (i.e. an observed undetectable rate of 0.44 or greater), we will reject the null hypothesis. We propose

a single stage design due to the length of follow-up required to assess this outcome. Patients who are inevaluable (defined in Section 12.1) will be replaced up to a possible total enrollment of 53 patients.

12.3 ANALYSIS APPROACHES

Primary objective: We will perform a one-sided exact binomial test based on a null undetectable rate of 0.32. If the p-value is less than 0.0503, we will reject the null hypothesis. With a sample size of 50, this corresponds to at least 22 patients with undetectable PSA at 10 months. The proportion of patients with undetectable PSA at 10 months will be estimated with a 90% confidence interval.

Secondary objectives:

Undetectable PSA at 6 months. The proportion of patients with undetectable PSA at 6 months will be estimated with a 90% confidence interval.

Toxicity: All adverse events will be tabulated by type and grade. Those that are possibly or probably related to study treatment. We will also tabulate possibly and probably related events that occur in the first 4 cycles docetaxel. Proportions of grade 3 and 4 events will be calculated with 95% confidence intervals.

Frequency of disease progression within the first four cycles of docetaxel: The proportion of patients with disease progression (defined in Section 11.2.3) will be calculated with a 95% confidence interval. Kaplan-Meier curves will be used to describe time to disease progression.

Frequency of PSA response: The proportion of patients with a PSA response within the four cycles of upfront docetaxel will be calculated with its exact 95% confidence interval.

Progression-free survival, Overall survival, and Time to development of castration resistance: All time to even outcomes will be described using Kaplan-Meier curves. The median time-to-event will be reported with its 95% confidence interval. If the median is not reached at the time of data analysis, a landmark time will be selected and the estimated survival fraction at the landmark time will be reported with its 95% confidence interval.

Exploratory objectives:

Serial genomic changes: Changes in genomic measures will be calculated and evaluated in relation to detectable PSA at 10 months using proportions. Regression approaches (e.g. logistic and Cox regression) will evaluate association between patients with genomic changes binary outcomes (e.g. undetectable PSA at 6 months) and time to event endpoints (e.g. PFS).

PSA kinetics: PSA will be evaluated over time using graphical displays ('spaghetti plots') and to determine if there are patients that hover just above or below the PSA = 0.2 ng/mL limit. Longitudinal linear modeling, estimated using GEE, will be used to describe trends in PSA over time. Additionally, we will consider (as sensitivity analyses) different PSA cutoffs

(e.g. 0.1 or 0.4 ng/mL) to determine the effects in inferences. Our hypothesis is that the inferences will not be sensitive to the cutoff.

12.4 INTERIM ANALYSES

The primary endpoint is evaluated at 10 months. As such, the time it takes to measure the events makes an interim analysis for futility or efficacy infeasible. With an anticipated uniform accrual within 24 months, corresponding to about two patients per month, at 75% of accrual (18 months), only about 16 patients will have been followed for 10 months. As such including an interim look for early stopping of accrual for futility is not feasible.

Accrual and evaluability of patients (e.g. drop-out) will be monitored continuously throughout the trial. Plans are in place for recruiting additional sites if accrual performs significantly worse than expected within the first 6 months of accrual. Specifically, accrual rates will be evaluated every 6 months by the study team. If the accrual rate is less than 70% of anticipated, corrective actions will be taken.

13 CORRELATIVE STUDIES

13.1 GENOMICS/GUARDANT®ANALYSIS

13.1.1 Description of the Assay

Guardant360 is a cell-free circulating tumor DNA (ctDNA) targeted next-generation sequencing (NGS) panel. It is an advanced diagnostic laboratory test (ADLT) offered by a sole source Clinical Laboratory Improvement Amendments (CLIA)-certified and College of American Pathology (CAP)-accredited laboratory. This solid tumor profiling panel sequences 70 clinically actionable genes for single nucleotide variants and copy number variations in 16 genes with a simple blood test. The genes are selected because mutations in these genes have FDA-approved matched therapies or are eligible for late phase clinical trials. The panel also includes genomic markers of acquired resistance that may require a change in pharmacotherapy.

13.1.2 Assay Methodology

The Guardant360 ctDNA next generation sequencing assay identifies single nucleotide variants (SNVs) in 70 genes and includes complete exon coverage of 30 genes and coverage of partial exons (“hot exons”) in 40 genes, including copy number variants in 16 genes. The gene list was selected to focus on those genomic alterations that are currently actionable defined as being targets of sensitivity or resistance to an FDA-approved matched therapy and/or a targeted therapy in clinical trials. The test simultaneously sequences the 70 cancer-related genes to an average depth of coverage of greater than 10,000X. To summarize, cell-free DNA is extracted from plasma and genomic alterations are analyzed by massively parallel paired end synthesis-by-sequencing of amplified target genes utilizing an Illumina Hi-Seq 2500 platform complemented by systematic end-to-end process optimization including conversion of cell-free DNA fragments into digital sequences, improvements in the Illumina next generation sequencing process itself, followed by bioinformatics algorithms which enable ctDNA to be measured as a quantitative percentage of total cell-free DNA.
Two 10mls of whole blood are collected in Streck Cell-Free DNA Blood Collection

(Streck) tubes, which contain a proprietary formaldehyde-free preservative in that stabilizes white blood cells, preventing the release of genomic DNA and allowing shipping and stability for seven days without need for refrigeration, cold bricks or preliminary centrifugation prior to shipping.

After digital libraries are produced, the sample is sequenced and post-sequencing data is processed using bioinformatics algorithms to quantify the absolute number of unique DNA fragments at a given nucleotide position. This proprietary process is referred to as Digital Sequencing™ and enables reporting of the fractional concentration (mutant allele frequency) of a given SNV. Circulating cell-free DNA is mostly derived from leukocyte lysis (germline) and generally a much smaller amount of tumor DNA is derived from cancer cell apoptosis/necrosis. All of the cell-free DNA fragments, including leukocyte-derived and tumor-derived, are simultaneously sequenced with up to single molecule sensitivity. In other words, both tumor DNA and "normal"/germline DNA are sequenced and measured in the same sequencing assay. The fractional concentration or mutant allele frequency for a given mutation is calculated as the fraction of circulating tumor DNA harboring that mutation in a background of wild-type cell-free DNA fragments. The analytic sensitivity reaches detection of 1-2 single mutant fragments from a 10 ml blood sample.

Leveraging the ability of Digital Sequencing™ to absolutely quantify the number of unique DNA fragments in a sequenced sample, the copy number of a given gene in plasma may be ascertained. To determine the copy number variant (CNV) or amplification of a given gene, the total number of unique fragments covering each gene are first measured. The mode of the normalized number of fragments covering each gene is calculated to estimate the fragment number corresponding to 2 copies to derive a baseline diploid value. All values of unique fragments for each gene are then normalized by this baseline value. The same procedure is employed using a large set of normal samples from healthy donors (Normal Set). The normalized concentration of a given gene in the sample is compared to its concentration in the Normal Set. The numerical result of the above procedure expresses the absolute copy number of a gene in plasma-derived cfDNA samples, which is a combination of both normal cell-free DNA (mainly leukocyte-derived) and tumor-derived gene copy number. Because most of the cell-free DNA is typically germline-derived, a small elevation in the gene copy number in plasma may reflect a much higher copy number in the tumor. For example, if the *ERBB2* (HER2 protein) gene copy number in the tumor was 10.0, and 5% of the DNA in cell-free DNA was tumor-derived and 95% was leukocyte-derived (germline copy number 2.0), then the *ERBB2* copy number in plasma would be 2.3.

13.1.13 Sample Acquisition

Patients will have two 10ml tubes of whole blood collected at baseline. This blood would be placed in two Streck Cell-Free DNA Blood Collection (Streck) tubes provided by Guardant in specimen kits. These kits will then be returned to Guardant at the address listed on the kit label.

14 ADVERSE EVENT REPORTING REQUIREMENTS

The descriptions and grading scales found in the revised NCI CTCAE version 4.0 will be utilized for AE reporting. In addition, SAEs have special reporting requirements. AE and SAE criteria and reporting requirements are outlined in this section. For both serious and non-serious adverse events, the investigator must determine the severity of the event, "expectedness" of the event, and the relationship of the event to study treatment administration.

The study period during which all AEs must be reported begins at time of informed consent and ends at end of study treatment. All SAEs, including death due to disease progression, must be reported up to 30 days after the end of study treatment. After this period, investigators should only report AEs that are attributed to Degarelix. SAEs should be monitored until they are resolved or are clearly determined to be due to the patient's stable or chronic condition or intercurrent illness(es). Patients removed from study for unacceptable AE(s) will be followed for AE(s) for 24 weeks or until resolution or stabilization of the AE if that takes more than 24 weeks.

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study treatment, and actions taken. All AEs should be recorded and described in the AE database in REDCap.

14.1 PURPOSE

AE data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AE are reported in a routine manner at scheduled times during a trial. Additionally, certain AEs must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe routine and expedited AEs reporting for this protocol.

Throughout the study, the Investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safety of the drug under investigation.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

14.2 DEFINITION OF ADVERSE EVENT

An AE is defined as any illness, sign or symptom which has appeared or worsened during the course of the study, regardless of causal relationship to the drug under study, experienced by a patient.

All adverse events should be recorded and described in the adverse event database in the REDCap data capture system.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency, duration or severity, or a change in the quality, of the disease or condition.

Only grade 3 or 4 abnormal lab values that were not noted during the Screening Phase should be recorded; however, any clinical consequences of the abnormality, regardless of grade should be reported as AEs.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Progression of cancer also will not be considered an AE.

Death should only be entered as the outcome for an AE when the patient's death is at least probably related to the AE (Note: the causal relationship of the AE to the test article is not to be considered in making this decision). If more than one AE is possibly related to the patient's death, the outcome of death should be indicated for each such AE.

14.3 DEFINITION OF SERIOUS ADVERSE EVENT

An SAE is defined by regulatory agencies as one that suggests a significant hazard or side effect, regardless of the investigator or sponsor's opinion on the relationship to investigational product. This includes, but may not be limited events that result in the following outcomes:

- Death
- Life-threatening. Patient was at substantial risk of dying at the time of the event or use or continued use of the medical product may have resulted in the death of the patient.
- Hospitalization (initial or prolonged). Report hospital admissions or prolongation of hospitalization. Emergency room visits that do not result in admission should be evaluated for one of the other serious outcomes.
- Disability or Permanent Damage. Report is the adverse event resulted in a substantial disruption of a person's ability to conducts normal life functions.
- Congenital anomaly/birth defect. Report if it is suspected that the exposure to the medical product prior to conception or during pregnancy may have resulted in an adverse outcome for the child.
- Other Serious or important medical events. If the event does not fit other outcomes, but may jeopardize the patient and may require intervention to prevent one of the other outcomes.

14.4 DEFINITION OF SEVERITY

Adverse events will be graded according to the NCI CTCAE. If toxicities are not defined by the NCI CTCAE v. 4.0, the intensity of each adverse event should be graded as outlined below:

GRADE 1	MILD: Sign or symptom noticeable, but does not interfere with normal daily activities.
GRADE 2	MODERATE: Sign or symptom sufficient to interfere with normal daily activities.

GRADE 3 SEVERE: Sign or symptom is incapacitating, with inability to perform daily activities.

GRADE 4 LIFE-THREATENING: sign or symptom poses immediate risk of death to this patient.

14.5 DEFINITION OF RELATIONSHIP TO STUDY DRUG

The categories for classifying the Investigator's opinion regarding the relationship of an AE to the study drug are listed below.

Definitely related: An adverse event occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible. The event must be definite pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary and feasible.

Possibly related: An adverse event with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Not related: An adverse event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying diseases provide plausible explanations.

14.6 DOCUMENTATION OF ADVERSE EVENTS

The Investigator will monitor and/or ask about or evaluate AEs using non leading questions at each visit or evaluation. The occurrence of all AEs will be documented in the CRF with the following information, where appropriate:

- AE name or term
- When the AE first occurred (start date)
- When the AE stopped (stop date), (or an indication of "ongoing")
- How long the AE persisted (optional)
- Severity of the AE
- Seriousness
- Actions taken
- Outcome
- Investigator opinion regarding the relationship of AE to the study drug(s)

14.7 EXPECTED ADVERSE EVENTS

Expected adverse events are those events known to be associated with study treatment. Expected adverse events are listed in the protocol, investigator brochure, package insert or product label. Events should be classified as unexpected, expected or more frequent than expected.

14.8 FOLLOW UP OF PATIENTS WITH ADVERSE EVENTS

The Investigator will follow patients with AEs, even if the patient was withdrawn from the study due to the AE, until the adverse event has:

- resolved
- the patient has returned to baseline state of health,
- the patient is lost to follow-up,
- the event is otherwise explained,
- the Investigator does not expect any further improvement or worsening of the adverse event.

Medically significant AEs considered related to the investigational product by the investigator or the sponsor will be followed until resolved or considered stable.

Any AEs not related to study drug ongoing at the time of completion of study drug should be considered unresolved.

14.9 NOTIFICATION OF SPONSOR OF SERIOUS ADVERSE EVENTS

Any serious adverse events which occur during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator.

Adverse events classified as serious require expeditious handling and reporting to IRBs and designated IRB or ethics board policies should be followed.

Within 24 hours of becoming aware of a SAE, the investigator must file an SAE report to MUSC **AND** Ferring Pharmaceuticals, Inc. .

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be submitted to MUSC and Ferring Pharmaceuticals within 24 hours of receipt.

SAEs will be submitted to MUSC via the 102509 (Gourdin) SAE Submission Form. A copy of that report should be downloaded and sent to Ferring Pharmaceuticals:

Fax: 1-877-243-8120 or
Email: safety.mailboxUS@ferring.com

15 ETHICAL AND REGULATORY CONSIDERATIONS

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

15.1 INFORMED CONSENT

The investigator or other designated personnel will obtain written informed consent from all participating patients or their authorized representatives. The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). These federal guidelines as well as ICH GCP must be followed when obtaining informed consent.

Copies of the signed document will be given to the patient and filed in the Investigator's study file, as well as the patient's medical record if in conformance with the institution's Standard Operating Procedures.

15.2 INSTITUTIONAL REVIEW

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

The trial will not be initiated without approval of the appropriate IRB. All administrative requirements of the governing body of the institution will be fully complied with. This protocol, consent procedures, and any amendments must be approved by the IRB in compliance with current regulations of the FDA. A letter of approval will be sent to the institution(s) funding the study prior to initiation of the study and when any subsequent modifications are made. The IRB will be kept informed by the Investigator as to the progress of the study as well as to any serious or unusual adverse events.

15.3 DRUG ACCOUNTABILITY

For each drug supplied for a study, an accountability ledger containing current and accurate inventory records covering receipt, dispensing, and the return of study drug supplies must be maintained. Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. These Accountability Forms must be readily available for inspection and are open to FDA or NCI inspection at any time.

15.4 PATIENT PRIVACY

In order to maintain patient confidentiality, all case report forms, study reports and communications relating to the study will identify patients by initials and assigned patient numbers. The FDA may request access to all study records, including source documentation for inspection. The Investigator/Institution will permit direct access to source data and documents by Ferring, its designee, the FDA and/or other applicable regulatory authority. The access may consist of trial-related monitoring, audits, IRB, and FDA inspections.

Subject medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The subject may request in writing that medical information be given to his/her personal physician.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

15.5 PUBLICATION POLICY

The Investigators plan to publish and present the information obtained from the study.

15.6 RECORD RETENTION

The Sponsor-Investigator must ensure maintenance of all study records per applicable federal regulations.

16 MONITORING

The SIS Unit will be responsible for the monitoring of study patient data and records; monitoring will be performed centrally. The SIS Unit will be responsible for forwarding any applicable reports to the HCC DSMC for review.

The SIS Unit will conduct patient eligibility audit reviews for all patients at each participating center prior to patient registration. During the course of the study, each site will be selected for an audit approximately once a year. Progress reports will be submitted to the HCC DSMC approximately twice a year.

The SIS Unit will maintain a shadow regulatory binder for all participating centers. Required regulatory documents, including those needed for site initiation, during activation, and study closure, are outlined in the operations manual for this study.

16.1 PROTOCOL DEVIATIONS

For the purposes of this study, a **protocol deviation** is any variance from the protocol involving a subject or subjects that is not approved by the IRB prior to its initiation or implementation, and occurs when a member of the study team departs from the IRB-approved protocol in any way without the investigator first obtaining IRB approval. Protocol Deviations have special reporting requirements.

Any protocol deviation and any supporting documentation will be submitted to the SIS Unit by the site within 10 days of notification as outlined in the IIT SOP for this study. Local IRB reporting requirements should be followed. Any IRB approvals or acknowledgments should be submitted to the SIS Unit.

16.2 DATA SAFETY MONITORING BOARD

The HCC DSMC will have oversight of the protocol. The HCC DSMC will meet at a minimum on a semi-annual basis to review the audits and progress reports for this IIT.

In addition, all protocol deviations and SAEs as defined above will be reviewed by the HCC DSMC at monthly meetings. As new protocol deviations or serious adverse events are reported to the SIS Unit, the SIS Unit will review these reports for form completion and follow up if more information is warranted. The SIS Unit will forward the event report to the HCC DSMC so that the information can be reviewed at the next available DSMC meeting. During the DSMC review, the DSMC can make recommendations for any further study action. The SIS Unit will maintain a copy of the DSMC approval letters for each event

reviewed for this study within the site's central study file and will distribute to the participating site, if applicable.

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APPENDIX A: CALCULATION OF CREATININE CLEARANCE

Estimation of creatinine clearance using Cockroft and Gault method:

$$Cl_{CR} \text{ for males (mL/min)} = \frac{[140 - \text{age (years)}] \text{ X } [\text{weight (kg)}]}{(72) \text{ X } [\text{Serum creatinine (mg/dL)}]}$$

APPENDIX B: ADVERSE EVENTS ASSOCIATED WITH THE USE OF DOCETAXEL IN THE TAX327 TRIAL

Table 4. Adverse Events of Any Grade, or of Grade 3 or 4, That Occurred or Worsened during Treatment.

Adverse Event	Docetaxel Every 3 Wk (N=332)	Weekly Docetaxel (N=330)	Mitoxantrone Every 3 Wk (N=335)
		percent	
Grade 3 or 4 anemia	5	5	2
Grade 3 or 4 thrombocytopenia	1	0	1
Grade 3 or 4 neutropenia	32*	2†	22
Febrile neutropenia	3	0	2
Impaired LVEF‡	10†	8†	22
Major decrease	1†	2*	7
Fatigue	53†	49†	35
Grade 3 or 4	5	5	5
Alopecia	65†	50†	13
Nausea, vomiting, or both	42	41	38
Diarrhea	32†	34†	10
Nail changes	30†	37†	7
Sensory neuropathy	30†	24†	7
Anorexia	17	21*	14
Change in taste	18†	24†	7
Stomatitis	20†	17†	8
Myalgia	14	14	13
Dyspnea	15*	14*	9
Tearing	10†	21†	1
Peripheral edema	19†	12†	1
Epistaxis	6	17†	2
≥1 Serious adverse event	26	29	20
Treatment-related death	0.3	0.3	1

* P≤0.05 by Fisher's exact test for the comparison with the mitoxantrone group.
† P≤0.0015 by Fisher's exact test for the comparison with the mitoxantrone group. A Bonferroni adjustment for multiplicity was used to obtain the nominal significance level of 0.0015 (approximately 0.05÷34), on the basis of two tests being carried out on the 17 adverse events, with at least 20 events in at least one of the three treatment groups.
‡ A major decrease in the left ventricular ejection fraction (LVEF) was defined as a decrease of at least 10 percent in the absolute value to below the lower limit of the normal range.

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