Official Title:	A Pilot Study of Docetaxel and Carboplatin for treatment of patients with metastatic, castration resistant prostate cancer containing biallelic inactivation of genes in the BRCA1/2 pathway
NCT number:	NCT02598895
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Date of the Document:	June 8, 2022

Clinical Study Protocol

Study Title:	A Pilot Study of Docetaxel and Carboplatin for treatment of patients with metastatic, castration resistant prostate cancer containing biallelic inactivation of genes in the BRCA1/2 pathway
Study Number:	9381
Study Phase:	Pilot
Product Name:	Docetaxel and Carboplatin
IND Number:	not applicable
Indication:	Treatment of metastatic, castration resistant prostate cancer containing biallelic mutations of genes in the BRCA1/2 pathway
Study sites	University of Washington, Fred Hutchinson Cancer Center
Investigators	Principal investigator: Heather Cheng, M.D., Ph.D. Co-Investigators: Robert Bruce Montgomery, M.D. Andrew Hsieh, M.D. Elahe Mostaghel, M.D., Ph.D. Peter Nelson, M.D. Michael Schweizer, M.D. Evan Yu, M.D. James Drechsler PA-C Tanisha Mojica, ARNP Katie Nega, ARNP
Protocol version	Current Version Date: 04.22.2022

STUDY OBJECTIVES:

Primary Objective:

- To determine the PSA response to docetaxel and carboplatin in the treatment of patients with metastatic CRPC containing biallelic inactivation of the homologous DNA repair (BRCA1/2) pathway, including BRCA1, BRCA2 and ATM.

Secondary Objectives:

- To assess maximal PSA response to docetaxel and carboplatin
- To assess PSA response duration to docetaxel and carboplatin
- To assess response of measurable disease
- To assess time to progression of bone lesions or measurable disease (RECIST 1.1)
- To correlate the presence of DNA repair pathway mutations in circulating tumor cells (CTC) and cell free DNA with the presence of mutations in tumor biopsy.

METHODS:

This is a pilot study of the combination of docetaxel and carboplatin in patients whose tumors are found to contain biallelic inactivation of genes in the BRCA1/2 pathway, including BRCA2, BRCA1 and ATM.

Patients will be treated with docetaxel (60 mg/m^2) and carboplatin (AUC 5) every 21 days until progression or unacceptable toxicity. Progression will be determined by PSA, CT chest/abdomen/pelvis and bone scan per Prostate Cancer Working Group 2 (PCWG2) criteria.

Number of Patients: 14 or more

Inclusion Criteria:

Patients meeting the following inclusion criteria will be eligible to participate in this study:

1. Signed informed consent form (ICF) providing agreement to adhere to the dosing schedule, report for all trial visits and authorization, use and release of health and research trial information
2. Male age > 18 years
3. Histologically or cytologically confirmed adenocarcinoma of the prostate (excluding neuroendocrine differentiation and small cell histology)
4. Ongoing gonadal androgen deprivation therapy with gonadotropin-releasing hormone (GnRH) analogues, antagonists or orchiectomy. Patients who have not had an orchiectomy must be maintained on effective GnRH analogue/antagonist therapy
5. Castration resistant prostate cancer as defined by serum testosterone < 50 ng/ml and one of the following:
   - PSA level of at least 2 ng/ml that has risen on at least 2 successive occasions at least 1 week apart.
   - Evaluable disease progression by modified RECIST 1.1 (Response Evaluation Criteria in Solid Tumors)
   - Progression of metastatic bone disease on bone scan with > 2 new lesions
6. Presence of metastatic disease on bone or CT scan
7. Prior therapy with abiraterone, enzalutamide and/or docetaxel. There is no limit to the number of prior treatment regimens.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1
9. Presence of biallelic inactivation of BRCA1, BRCA2, ATM (see section 1.1)

and/or Patients with clearly deleterious mutations of other genes involved in homologous DNA repair may be included at the investigator's discretion.

Exclusion Criteria:

Patients meeting any of the following exclusion criteria are NOT eligible:

1. Currently receiving active therapy for other neoplastic disorders will not be eligible.
2. Histologic evidence of neuroendocrine or small cell carcinoma of the prostate will not be eligible.
3. Known parenchymal brain metastasis
4. Active or symptomatic viral hepatitis or chronic liver disease
5. Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II-IV heart disease or cardiac ejection fraction measurement of <35 % at baseline
6. Treatment with an investigational therapeutic within 30 days of Cycle 1.
7. Presence of dementia, psychiatric illness, and/or social situations limiting compliance with study requirements or understanding and/or giving of informed consent.
8. Any condition(s), medical or otherwise, which, in the opinion of the investigators, would jeopardize either the patient or the integrity of the data obtained.

CRITERIA FOR EVALUATION

Anti-Tumor Effects:

- The percentage of patients achieving ≥50% reduction in PSA according to PCWG2 criteria.
- The percentage of patients achieving ≥90% reduction in PSA according to PCWG2 criteria.
- The percentage of patients achieving ≥30% reduction in measurable disease by RECIST 1.1.
- Median time to tumor progression by PCWG2 criteria.

STATISTICAL METHODS:

Efficacy:

The proportion of patients with PSA decline by 50% from baseline (PSA_{50}) will be evaluated. The primary efficacy endpoint is the percent of patients achieving PSA_{50} with docetaxel and carboplatin. The historical comparison is a PSA_{50} of 26%. The target response rate is 60%. The study will follow an optimal two-stage Simon design (Simon, 1989) where the null hypothesis that the true PSA response rate (PSA decline by 50% from baseline) is 0.26 will be tested against a one-sided alternative.

We will use a Simon minimax 2-stage design, which will allow early stopping for futility after the first stage if the response rate is low. Our null and alternative hypotheses are H0: $p \leq 26\%$ vs. H1: $p \geq 60\%$. The minimax 2-stage design for these parameters requires a first stage enrolling 5 patients. If 1 of the first 5 patients achieves a **PSA_{50}** response, H0 cannot be rejected. If ≥1 of 5 patients respond, enrollment in that cohort continues until 14 patients have completed the trial, and the response rate is calculated for all 14 patients. If ≤6 of 14 patients have a **PSA_{50}** the null hypothesis cannot be rejected. This design will provide 80% power to detect a **PSA_{50}** rate of 60% (one-sided $\alpha=0.05$). This design also provides a 60% probability of early stopping if H0 is true, affording protection against treating more patients than necessary if the treatment is not effective.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
BUN	Blood urea nitrogen
C	Celsius
CBC	Complete blood count
CR	Complete response
cfDNA	Cell free DNA
CrCl	Creatinine clearance
CPK	Creatinine phosphokinase
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTC	Circulating Tumor Cells
ECG	Electrocardiogram
F	Fahrenheit
FDA	Food and Drug Administration
GCSF	Granulocyte stimulating factor
GLP	Good Laboratory Practice
Hct	Hematocrit
Hgb	Hemoglobin
HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonisation
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board

LDH	Lactic dehydrogenase
LLN	Lower limit of normal
LN	Lymph node
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
PD	Progressive disease
PFS	Progression free survival
PR	Partial response
PT	Prothrombin time
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
SOC	System Organ Class
SRS	Special reporting situations SUSAR

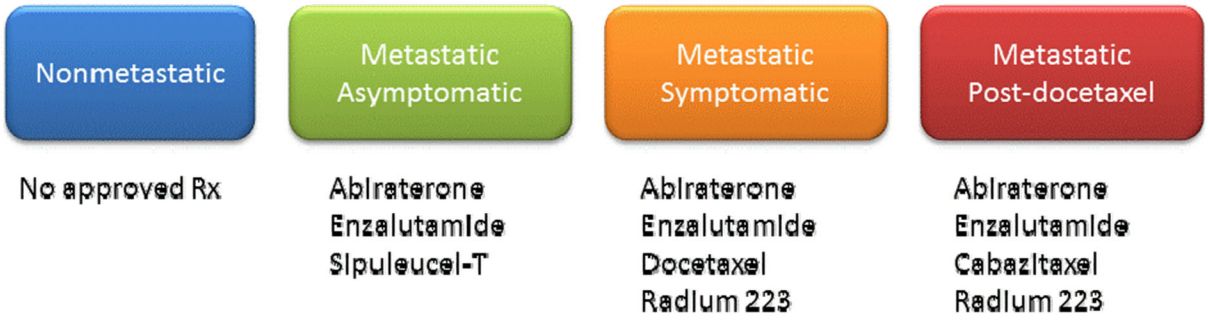
Suspected unexpected adverse event reporting

ULN	Upper limit of normal
WBC	White blood cell (count)

1 INTRODUCTION

1.1 Therapy for metastatic, castration resistant prostate cancer (CRPC)

Prostate cancer is the most common cancer among men with approximately 220,000 new cases per year in the United States alone. Roughly 10-20% of patients present with metastatic disease, and 40% of patients relapse after surgery or radiation therapy for presumed localized disease.
While androgen-deprivation therapy for advanced prostate cancer is usually initially effective, almost all tumors eventually become castration resistant after a median of 18-24 months. The currently FDA approved therapies for metastatic CRPC include: docetaxel (Taxotere), the AR targeting agents abiraterone (Zytiga) and enzalutamide (Xtandi) prior to or after docetaxel, radium 223 (Xofigo) for patients declining docetaxel or after docetaxel, sipuleucel-T (Provenge) prior to or after docetaxel, and cabazitaxel (Jevtana). Thus, there are many new treatment options for men with metastatic CRPC. One major challenge for the field is to identify subsets of patients whose cancer biology is distinct and may disproportionally benefit from treatment regimens that would otherwise not be considered.



In current clinical practice most patients receive either abiraterone or enzalutamide, and often radium 223, prior to docetaxel in the metastatic CRPC setting.
The second-generation AR-targeting agents abiraterone and enzalutamide are FDA-approved prior to docetaxel in patients with metastatic CRPC. No prospective studies have been performed with docetaxel after either agent, and these are unlikely to be carried out given the cost and lack of industry sponsor. Single institution series suggest that treatment of prostate cancer with abiraterone prior to docetaxel reduces PSA response rates and progression free survival (PFS) to docetaxel [1]. These results compare to the phase III registration studies of docetaxel (TAX-327) in which PSA_{50} was 45-50%, PFS 6 months and median OS of 18-19 months {Petrylak, 2004 #2233, Tannock, 2004 #2882).

Together, these suggest that in the current treatment environment docetaxel is significantly less efficacious than has been reported in the registry studies, highlighting the need for approaches to improve docetaxel efficacy

Regimen	Indication	PSA50	PFS	OS	Reference
Docetaxel	mCRPC 1st line	45%	NA	18.9 mos	Tannock
Docetaxel	mCRPC 1st line	50%	6 mos	18 mos	Petrylak
Docetaxel after Abi	mCRPC 1st line	26%	4.6 mos	12.5 mos	Mezynski
Docetaxel after Abi	mCRPC 1st line	38 vs. 63%	4.4 mos	NA	Schweizer

1.2 Sensitivity and resistance of CRPC to DNA damaging agents

The first chemotherapeutic agent FDA approved for the treatment of CRPC was the DNA- damaging anthracycline, mitoxantrone {Tannock, 1996 #2883}. Subsequent studies of the use of Satraplatin, a platinum agent in phase III randomized studies as second line chemotherapy (including after docetaxel) demonstrated a significant improvement in progression free survival (HR 0.67, PFS 11 weeks, PSA_{50} 25%) [2]. Based on this evidence, investigators hypothesized that combining the DNA damaging agent carboplatin with docetaxel could improve efficacy. A
CALGB phase II study of the combination of docetaxel and carboplatin with estramustine induced a PSA50 response rate of 68% with progression free survival of 8 months [3].
Estramustine is no longer considered because not only did it fail to improve response or survival compared to docetaxel alone, but it also added significant toxicity. Later studies indicated that combination therapy with a DNA damaging platinum and docetaxel improved response in previously treated tumors mCRPC[2]. In patients with tumors refractory to docetaxel, the addition of carboplatin has been reported to result in a PSA_{50} rate of 18% and PFS of 3 months [4]. These results provide evidence that combining the DNA damaging agent carboplatin with docetaxel could improve efficacy, particularly in the right tumor context, such as known sensitivity to DNA-damaging agents such as platinums and anthracyclines.

Activity of carboplatin with docetaxel in prostate cancer						
Docetaxel/carboplatin	mCRPC line	nd	18%	3 mos	12 mos	Ross
Docetaxel/EMP carboplatin	mCRPC line	1st	68%	8 mos	19 mos	Oh

Platinum compounds, such as carboplatin and cisplatin, are believed to exert their anti-tumor effects through crosslinking of DNA, which in turn inhibits DNA synthesis and repair. As a result, tumors with defects in DNA repair, and those with mutations in homologous recombination mutations such as BRCA1/2-Fanconi anemia pathway genes are particularly sensitive to platinum agents and poly-ADP-ribose polymerase inhibitors (PARPi). The relationship between BRCA1/2-Fanconi anemia pathway and platinum sensitivity is well- described in breast and ovarian cancers[5,6].

The relationship between DNA-damaging cytotoxic chemotherapies such as platinums and anthracyclines and modest response in earlier prostate cancer trials suggests that an as-yet unidentified subset of patients benefitted most from treatment due to specific tumor biology. We believe this is a subset of patients with defects in homologous recombination DNA damage repair pathway genes.

1.3 BRCA2 and DNA damage repair pathway genes in CRPC.

Very recent efforts have been underway to perform molecular profiling of metastatic, castration resistant prostate cancer as part of the SU2C Prostate Dream Team research study at UWMC/FRED HUTCHINSON CANCER CENTER (CC-IRB # 7917) to better characterize the molecular subtypes of mCRPC. Indeed, current analyses have revealed approximately **20% of CRPC metastatic tumors contain biallelic inactivation of BRCA1, BRCA2 or ATM** (De Bono, unpublished). In approximately half of these cases, inactivation results from heterozygous copy loss in combination with a germline mutation, whereas in the other half of tumors inactivation results from homozygous copy loss. Most mutations identified thus far are in the BRCA2 gene, but mutations have also been identified in BRCA1, ATM, and other BRCA1/2-Fanconi anemia pathway genes (De Bono, unpublished data). Thus, the 20% of patients

with mCRPC whose tumors harbor biallelic inactivation of BRCA1/2, ATM and other DNA repair enzymes may be the subset with increased sensitivity to treatment with DNA-damaging agents such as carboplatin in the earlier studies of unselected patients with mCRPC described above.

1.4 Response to DNA damaging agents in tumors with biallelic inactivation of BRCA2.

We have identified three patients from UW/FRED HUTCHINSON CANCER CENTER who tumors contain biallelic inactivation in one of these three genes using either UW-Oncoplex or UWMC sequencing and have been successfully treated with regimens containing DNA damaging agents, either docetaxel with carboplatin (60 mg/m^2 and AUC 5 every 21 days, 2 patients) or doxorubicin with carboplatin (1 patient). Two of the patients were treated with first-line docetaxel, one of whom was primarily refractory to docetaxel. All three patients experienced significant PSA responses.

- Patient 1 developed liver metastasis, had a limited response docetaxel, and no response to abiraterone and enzalutamide, and was ultimately treated with two prolonged cycles of docetaxel and carboplatin.
- Patient 2 was treated docetaxel/carboplatin with complete response in his metastatic liver disease and subsequently treated with "maintenance" carboplatin and achieved *two years* of progression free survival.

Patient 3 was refractory to abiraterone and docetaxel and was treated with doxorubicin and carboplatin by his local oncologist based on the knowledge of his BRCA2 sequencing results and has achieved a greater than 50% PSA decline (PSA_{50}).

In summary, 3 of 3 UWMC/FRED HUTCHINSON CANCER CENTER patients with tumors containing biallelic BRCA2 inactivation achieved dramatic and sometimes very prolonged clinical responses to DNA damaging agents despite poor prognostic features such as liver metastases and failure of first-line docetaxel and second line hormonal agents. One case series of germline BRCA mutations carriers (unselected for biallelic loss) included a germline BRCA2 carrier with prostate cancer treated with docetaxel/carboplatin who survived for *37 months*[7]. Our experience suggests the possibility that 1 in 5 metastatic castration resistant prostate cancer tumors containing biallelic inactivation of BRCA1, BRCA2 or ATM and will be exquisitely sensitive to DNA damaging agents such as carboplatin and doxorubicin.

Therefore, **in this study we propose to prospectively assess response to the combination of docetaxel and carboplatin in patients with mCRPC whose tumors contain biallelic inactivation of BRCA1, BRCA2 or ATM and have progressed after any succession of front-line agents.** Sequencing results may be procured through UW-Oncoplex, SU2C or other commercial sequencing assays (e.g., Foundation One). If the true rate of response is 80% or higher (the anticipated result) in the prospective patient population, a very limited number of patients will be needed to demonstrate statistically significant superiority over docetaxel alone after any front-line agents (PSA_{50} of 26%)[1].

Of note, an ovarian cancer study applied massively parallel sequencing of 390 tumors and identified germline and somatic mutations not only in BRCA1, BRCA2 and ATM, but also in 10 other homologous recombination genes (BARD1, BRIP1, CHEK1, CHEK2, FAM175A, MRE11A, NBN, PALB2, RAD51C and RAD51D) were associated with platinum response and survival[8]. If results from the proposed study are positive, we propose to expand the eligibility to include mCRPC with loss of other DNA repair genes.

If this study successfully demonstrates significant responses to DNA damaging agents in this meaningful subset of patients with mCRPC, there would be clear rationale for follow up studies aimed at further disruption of DNA repair pathway. Potential approaches would include chemotherapy followed by maintenance therapy with PARP inhibitors, more intensive regimens of DNA damaging

agents (anthracyclines with platinum) and/or immediate alternative effective chemotherapy regimens in treatment of an estimated 1 in 5 men with mCRPC.

1.1 Docetaxel and carboplatin

Docetaxel (Taxotere) and carboplatin (Paraplatin) are synthetic antineoplastic agents extensively used in the treatment of solid tumors. Commercial sources will be used for this study.

1.5.1 Drug toxicity

Toxicity of docetaxel includes:

- Allergic Reaction. Hypotension, urticaria, and hypersensitivity are reported. Premedication with dexamethasone is required.
- Hematologic Taxanes including docetaxel alone and in combination with other antineoplastic agents, have been associated with neutropenia, anemia, and thrombocytopenia.
- Neurologic – neuropathy is reported in over 10% of patients
- Dermatologic: Alopecia (56% to 76%), dermatological reaction (20% to 48%; severe: ≤5%), nail disease (11% to 41%)
- Endocrine & metabolic: Fluid retention (13% to 60%; severe: 7% to 9%; dose dependent)
- Gastrointestinal: Stomatitis (19% to 53%; severe 1% to 8%), diarrhea (23% to 43%; severe: 5% to 6%), nausea (34% to 42%), vomiting (22% to 23%)
- Hepatic: Increased serum transaminases (4% to 19%). If bilirubin > ULN, or if AST and/or ALT > 1.5 × ULN concomitant with alkaline phosphatase > 2.5 × ULN docetaxel should not be administered.
- Neuromuscular & skeletal: Weakness, myalgia and arthralgia are reported in greater than 10% of patients.
- Ophthalmic: Epiphora (associated with canalicular stenosis ≤1% with every 3-week administration)

Toxicity of carboplatin includes:

- Endocrine & metabolic: Hyponatremia (29% to 47%), hypomagnesemia (29% to 43%), hypocalcemia (22% to 31%), hypokalemia (20% to 28%)
- Gastrointestinal: Vomiting (65% to 81%), abdominal pain (17%), nausea (without vomiting: 10% to 15%)
- Hematologic & oncologic: Bone marrow depression (dose related and dose limiting; nadir at ~21 days with single-agent therapy), anemia (3/4: 21%), leukopenia (grades 3/4: 15% to 26%), neutropenia (grades 3/4: 16% to 21%), thrombocytopenia (grades 3/4: 25% to 35%)
- Hypersensitivity: Hypersensitivity (2% to 16%)
- Renal: Decreased creatinine clearance (27%), increased blood urea nitrogen (14% to 22%)
- Central nervous system: Peripheral neuropathy (4% to 6%), neurotoxicity (5%)
- Dermatologic: Alopecia (2% to 3%),

1.5.2 Supplier

Commercial supplies of docetaxel and carboplatin will be used.

1.5.3 Rationale for study design

The combination of docetaxel and carboplatin has activity as first and second line therapy for patients with CRPC. In the very small number of patients at the UWMC/FHCRC for whom tumor sequencing has revealed biallelic inactivation, 3 out of 3 patients have responded to a carboplatin-containing regimen. Because the combination of docetaxel and carboplatin has been previously tested, has known efficacy and toxicity data for patients with CRPC, it is the most appropriate regimen for testing.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To assess rate of 50% PSA decline to docetaxel and carboplatin.

2.2 Exploratory Objectives (Phase 2)

- To assess PSA response duration to docetaxel and carboplatin
- To assess response of measurable disease
- To assess time to progression of bone lesions or measurable disease (RECIST)
- To assess response to docetaxel and carboplatin in tumors with mutation of DNA repair pathway genes (BRCA1, BRCA2, ATM)
- To correlate the presence of DNA repair pathway mutations and copy number alterations in metastatic tissue versus in circulating tumor cells (CTC) and cell free DNA
- To correlate changes in CTC number with PSA and radiographic response

3 INVESTIGATIONAL PLAN

3.1 Overall study design and plan

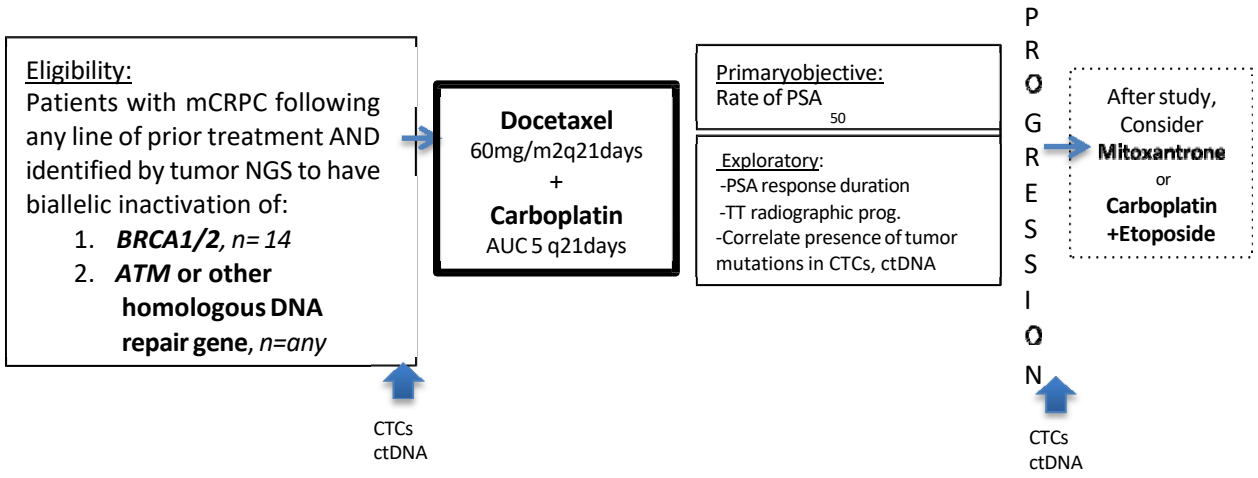
This is an open-label study with a single Pilot component. Patients will

remain on treatment until any of the following occur:

- unacceptable toxicity
- documented progression by radiographic imaging
- completion of 10 cycles of therapy (Note: Additional cycles permitted at the investigator's discretion if patients are responding and there is no evidence of cardiomyopathy or other toxicities).
- achievement of complete response (CR) per RECIST 1.1 criteria

RECIST 1.1: (See Appendix). Baseline CT or MRI of the abdomen/pelvis and chest film or chest CT will be performed during screening and every 3 months, or as clinically indicated.

Bone Scan: Baseline bone scan will be performed during screening and every 3 months, or as clinically indicated.



4 STUDY POPULATION SELECTION

4.1 Study Population

Study subjects will be recruited from the Fred Hutchinson Cancer Center and University of Washington (UW), which are separate sites within the same practice and share a single IRB.

Eligible patients will be identified by their medical oncologist, who will discuss the study with the patient. If a patient is interested in participating, he will be appropriately counseled and informed consent will be obtained by one of the investigators. A total of 14 or more subjects will be enrolled in the study.

4.2 Inclusion Criteria

Patients meeting the following inclusion criteria will be eligible to participate in this study:

1. Signed informed consent form (ICF) providing agreement to adhere to the dosing schedule, report for all trial visits and authorization, use and release of health and research trial information.
2. Age $\geq$ 18 years.
3. Histologically or cytologically confirmed carcinoma of the prostate (excluding neuroendocrine differentiation or squamous cell histology).
4. Ongoing gonadal androgen deprivation therapy with gonadotropin-releasing hormone (GnRH) analogues, antagonists, or orchiectomy. Patients who have not had an orchiectomy must be maintained on effective GnRH analogue/antagonist therapy.
5. Castration resistant prostate cancer as defined by rising PSA when serum testosterone <50ng/ml (note: current testosterone results are not required if the potential subject has not missed any GnRH analogue/antagonist doses since their last result was received) AND one of the following:
   - PSA level of at least 2 ng/ml that has risen on at least 2 successive occasions at least 1

- Evaluable disease progression by modified RECIST (Response Evaluation Criteria in Solid Tumors).
- Progression of metastatic bone disease on bone scan with > 2 new lesions.

6. Prior therapy with abiraterone, enzalutamide and/or docetaxel. There is no limit to the number of prior treatment regimens.
7. Presence of metastatic disease on scans.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1.
9. Life expectancy ≥12 weeks.
10. No prior malignancy is allowed except:
    - Adequately treated basal cell or squamous cell skin cancer or
    - In situ carcinoma of any site or
    - Other adequately treated malignancy for which the patient has been disease-free for at least one year (any prior chemotherapy is allowed).
11. Patients must have adequate organ and marrow function as defined below obtained within 14 days prior to registration:
    - Absolute neutrophil count ≥1.5 x 10^9 cells/L
    - Hgb ≥ 9.0 g/dL
    - Platelets ≥100,000 x 10^9/L
    - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin levels ≤ 1.5 x ULN
12. Patients must have clear and documented evidence of biallelic inactivation BRCA1, BRCA2 or ATM by sequencing, for example UW-Oncoplex, SU2C, or Foundation One testing.
and/or
Patients with clearly deleterious mutations of other genes involved in homologous DNA repair (e.g., PALB2, BRIP1, etc.) by sequencing via UW-Oncoplex, SU2C, or Foundation One testing may be included at the investigator's discretion.

4.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Currently receiving active therapy for other neoplastic disorders.
2. Histologic evidence of neuroendocrine or small cell carcinoma of the prostate.
3. Known parenchymal brain metastasis.
4. Active or symptomatic viral hepatitis or chronic liver disease.
5. Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II-IV heart disease or cardiac ejection fraction measurement of < 35 % at baseline, if done.
6. Treatment with an investigational therapeutic within 30 days of Cycle 1.
7. Patients with dementia/psychiatric illness/social situations limiting compliance with study requirements or understanding and/or giving of informed consent are not eligible
8. Any medical conditions, which, in the opinion of the investigators, would jeopardize either the patient or the integrity of the data obtained are not eligible.

5 STUDY TREATMENT(S)

5.1 Treatments Administered

5.1.1 Docetaxel and carboplatin

Please refer to the docetaxel and carboplatin package inserts for complete preparation and administration. Docetaxel and carboplatin should be administered over approximately 30-60 minutes per institutional standard.

Docetaxel 60 mg/m^2 will be administered on Day 1 of each 21-day cycle. Carboplatin AUC

5 will be administered on Day 1 of each 21-day cycle.

5.1.1.1 Docetaxel and carboplatin risks and precautions

Please refer to the package insert for docetaxel and carboplatin for all risks and precautions. The following are risks when docetaxel and carboplatin have been used in combination.

	Grade 3	Grade 4
Anemia	6%	0
Neutropenia	56%	6%
Thrombocytopenia	6%	0
Febrile neutropenia	3%	0
Infection	6%	0
Hyperglycemia	6%	0
Pain	6%	0
Renal insufficiency	3%	0

Ross et al.

5.1.2 Antiemetics

Dose modifications for nausea and vomiting should not be made until patients are on adequate doses of antiemetics. Docetaxel and carboplatin are classified as moderately emetogenic chemotherapeutic agents, with a frequency of emesis of 30-60%. Institutional guidelines for moderately emetogenic chemotherapy should be followed.

5.1.3 Growth Factors

Filgrastim (G-CSF), pegfilgrastim, sargramostim (GM-CSF), and other growth factors may be utilized at the discretion of the investigator. All growth factors must be recorded as concomitant medication. NCCN guidelines for use of growth factors and prophylactic antibiotics will be followed based on patient risks of neutropenia and infection[9].

5.1.4 Concomitant Therapy

Concurrent enrollment in another clinical investigational drug or device study is prohibited. Supportive care medications are permitted with their use following institutional guidelines.

5.1.5 Restrictions

The concurrent administration of other anticancer therapy, including cytotoxic or immunotherapy, is prohibited therapy. Use of other investigational drug therapy for any reason is prohibited. The decision to administer a prohibited drug/treatment will be made by the investigator based on the consideration of the safety of study participant.

5.2 Supply, Packaging and Storage

5.2.1 Docetaxel and carboplatin Supply, Packaging, Storage

Docetaxel and carboplatin are stored and administered per institutional protocol.

5.3 Investigational Product Retention and Accountability at Study Site

5.3.1 Dose modifications for hematologic toxicity

On day 1 of a cycle	**Dose**
ANC ≥1.5 x10^9 cells /L and platelet count ≥100 x 10^9 /L	100%
ANC <1.5 x10^9 cells /L and/or platelet count <100 x 10^9 /L	Delay docetaxel and carboplatin. Repeat CBC weekly. If ANC resolves to ≥1.5 x109 cells /L AND platelet count to ≥100 x 109/L, resume docetaxel and carboplatin at 100% of starting dose If treatment is delayed by more than 6 weeks, the patient should be removed from chemotherapy treatment. **(*If ANC and/or platelet count are outside of the range listed above but still considered within an acceptable range for standard of care range, the PI may determine that dosing may still occur at PI discretion.)**

At any time during a cycle	
Grade 3 febrile neutropenia (defined as an ANC <1.0 x 109 cells/L) and a single Temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour) **Documented infection with Grade 3 neutropenia (defined as an ANC <1.0 x 109 cells/L)** **Grade 4 neutropenia (defined as an ANC<0.5 x 109 cells/L lasting more than 5 days)**	Delay treatment until improvement of symptoms and resolution of the ANC to ≥1.5 x109 cells /L and platelet count to ≥100 x 109/L. Decrease BOTH docetaxel and carboplatin to 80% of starting dose for all subsequent cycles. With recurrence of any of these toxicities, consider removal from chemotherapy

Dose Modifications for Hepatic Toxicity

AST/ALT > 2-5 x ULN and AP < 2x ULN and bilirubin WNL	Delay treatment until recovery
AST/ALT > 2-5 x ULN and AP > 2.5-5 x ULN and bilirubin WNL	Delay treatment until recovery
AST/ALT > 5 x ULN and AP > 5 x ULN and bilirubin WNL	Delay treatment until recovery

5.3.2 Dose modifications for gastrointestinal toxicity

For Grade 4 nausea and vomiting **despite maximal antiemetic therapy**, delay docetaxel and carboplatin until symptoms have resolved to ≤Grade 2. When symptoms have resolved to ≤Grade 2, continue docetaxel and carboplatin at 100% of the current dose. If Grade 4 nausea and vomiting recur despite maximal antiemetic therapy, the patient should be removed from chemotherapy.

5.3.3 Dose modifications for cumulative docetaxel or carboplatin toxicity

For all patients who respond to combined study treatment of docetaxel and carboplatin (as assessed by PSA, restaging scans, and/or clinical improvement), treatment will continue until disease progression or unacceptable toxicities. **To improve tolerability and allow the patient to continue in the event of treatment response, the regimen may be modified per investigator discretion treatment in the following ways: If there are cumulative toxicities (such as fatigue, myelosuppression, or neuropathy), doses of either docetaxel and/or carboplatin may be reduced (up to 25%) and/or held (up to 6 weeks) OR patient may continue on single-agent carboplatin. If there is clinical response and cumulative toxicities to single agent carboplatin, doses may be reduced (up to 25%) and/or held (up to 6 weeks).**

6 STUDY PROCEDURES

6.1 Informed Consent

Written Informed Consent and Authorization must be obtained from the patient in accordance with local practice and regulations. The study will be discussed with the patient, and a patient wishing to participate must give written informed consent and Authorization for Use and Release of Health and Research Study Information prior to any study-related procedures or change in treatment.

A signed, Institutional Review Board/Ethics Committee (IRB) approved, informed consent must be obtained from patients before any study specific procedures can occur. Confirmation of the patient's informed consent and the informed consent process must also be documented in the patient's medical record.

A copy of the fully signed informed consents will be given to the patient.

6.2 Medical History

Medical history, such as previous treatments, procedures, and conditions will be collected during the screening period.

6.3 Physical Examination

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening and at EOT. Otherwise, directed physical exams are permissible.

6.4 Laboratory Tests

6.4.1 Clinical Safety Laboratory Tests

Clinical safety laboratory tests will be assessed as UWMC/FRED HUTCHINSON CANCER CENTER standard of practice. At a minimum, a complete blood count (CBC) and complete serum chemistry will be performed within 3 days of the first day of each cycle and thereafter as clinically indicated.

Clinical safety labs will include the following:

Table 9. List of Clinical Safety Laboratory Tests

Hematology: Hematocrit (Hct) Hemoglobin (Hgb) Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential **Liver Functions:** Alanine aminotransferase (ALT; SGPT) Aspartate aminotransferase (AST; SGOT) Alkaline phosphatase (ALK-P) Total bilirubin	**Serum Chemistry:** Albumin (ALB) Blood urea nitrogen (BUN) Calcium (Ca) Carbon dioxide (CO_2) Chloride (Cl) Creatinine Glucose Potassium (K) Sodium (Na) ***Additional laboratory tests:** Baseline Prothrombin Time (PT/INR) test for patients who are taking Coumadin while on study. Further monitoring per discretion of treating physician.

6.4.2 Research Labs

Please refer to the laboratory manual for details.

6.4.3 Sample Collection, Storage, and Shipping

The Fred Hutchinson Cancer Center and University of Washington clinical laboratories will analyze all hematology, blood chemistry samples collected for the study. Samples will be analyzed at a facility meeting Good Laboratory Practice (GLP) requirements and/or using methods documented in a methods validation report.

6.5 Criteria for Evaluation

6.5.1 Antitumor effects:

- The percentage of patients achieving ≥50% reduction in PSA according to PCWG2 criteria.
- The percentage of patients achieving ≥90% reduction in PSA according to the PCWG2 criteria.
- The percentage of patients achieving ≥30% reduction in measurable disease by RECIST.
- Median time to tumor progression by PCWG2 criteria

6.5.2 Statistical Methods:

The proportion of patients with PSA decline by 50% from baseline (PSA_{50}) will be evaluated. The primary efficacy endpoint is the percent of patients achieving PSA_{50} with docetaxel and carboplatin. The historical comparison is a PSA50 of 26%. The target response rate is 60%.

study will follow an optimal two-stage Simon design (Simon, 1989) where the null hypothesis that the true PSA response rate (PSA decline by 50% from baseline) is 0.26 will be tested against a one-sided alternative.

We will use a Simon minimax 2-stage design, which will allow early stopping for futility after the first stage if the response rate is low. Our null and alternative hypotheses are H0: p≤26% vs. H1: p≥60%. The minimax 2-stage design for these parameters requires a first stage enrolling 5 patients. If 1 of the first 5 patients achieves a PSA_{50} response, H0 cannot be rejected. If ≥1 of 5 patients respond, enrollment in that cohort continues until 14 patients have completed the trial, and the response rate is calculated for all 14 patients. If ≤6 of 14 patients have a PSA_{50} the null hypothesis cannot be rejected. This design will provide 80% power to detect a PSA_{50} rate of 60% (one-sided α=0.05). This design also provides a 60% probability of early stopping if H0 is true, affording protection against treating more patients than necessary if the treatment is not effective.

6.5.3 Tissue Endpoints:

Circulating tumor cells (CTCs) and cfDNA will be collected as per standard operating protocol (appendix).

6.6 Safety Assessments

All participants receiving investigational agents will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported to the investigator by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol and recorded prior to each course of therapy. Life-threatening toxicities should be reported immediately to the Protocol Chair and Institutional Review Board (IRB).

Safety assessments will include:

- Adverse events including laboratory adverse events will be graded according to the NCI CTCAE, version 4.0.
- Laboratory tests (CBC with differential, platelets, LFT's, chemistry)
- Vital Signs (blood pressure, heart rate, temperature, and weight)
- Physical exam
- ECOG performance status

6.7 Safety Data Collection, Recording and Reporting

All observed or volunteered adverse events regardless of causal relationship to study drug will be recorded on the adverse event page(s) of the case report form (CRF).

6.7.1 Definition of Adverse Event (AE)

An adverse event is defined in the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice as "Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment" (ICH E6:1.2). An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, diagnosis or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. For the purposes of this study, temporal association is defined as the time between the subject's informed consent signature through 28 days after the final dose of study medication.

AEs further include worsening of a pre-existing medical condition (e.g., diabetes, migraine headaches, gout, hypertension, etc.) which has increased in severity, frequency, or duration, or is associated with significantly worsened outcomes.

The investigator or a medically licensed designee must pursue and obtain information adequate to determine the following: Grade (CTCAE v4.0), Causality (relationship to GC and/or rapamycin) and Outcome. The investigator's assessment of Grade, any Intervention (medication, procedure, etc.), Causality and Outcome will be indicated by signature of the PI or designated physician on the adverse event CRF. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, or his/her designated representative.

Attribution is defined as the determination of whether an adverse event is related to a medical treatment or procedure. Attribution categories are as follows:

- *Unrelated:* The adverse event is clearly NOT related to therapy
- *Unlikely:* The adverse event is doubtfully related to therapy
- *Possible:* The adverse event may be related to therapy
- *Probable:* The adverse event is likely related to therapy
- *Definite:* The adverse event is clearly related to therapy

6.7.2 Adverse Drug Reaction (ADR)

A noxious and unintended response to any dose of the drug (or biological) product for which there is a reasonable possibility that the product caused the response. ''Reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the adverse event.

Suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event (21 CFR 312.23).

Suspected Unexpected Adverse Event Reaction (SUSAR) is defined as an AE that is not consistent in nature, severity, or frequency with the product information documented in the current package insert or in the protocol, consent form, and/or prior reports.

If the investigator or designee determines that an AE meets the criteria for classification as a Serious Adverse Event (SAE) or Suspected Unexpected Adverse Event Reaction (SUSAR), s/he will immediately notify the UW/FHCRC Cancer Consortium IRB, and FDA. See Section 6.7.3 for definition of SAEs and SUSARs, and 6.7.6 for reporting guidelines.

Interventions for pretreatment conditions (e.g., elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered adverse events.

6.7.3 Definition of a Serious Adverse Event

An adverse event or suspected adverse reaction is considered ‘‘serious’’ if, in the view of the investigator or a medically licensed designee, it results in any of the following outcomes:

- Death;
- a life-threatening adverse event;
  Life-threatening adverse event or life-threatening suspected adverse reaction.
  An adverse event or suspected adverse reaction is considered ‘‘life-threatening’’ if its occurrence places the patient or subject at immediate risk of death. This definition does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- is a suspected transmission of infectious agents by a medicinal product

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A hospitalization meeting the definition for “serious” is any in-patient hospital admission that includes a minimum of an overnight stay in a health care facility. Interventions for pretreatment conditions (e.g., elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered SAE/SUSARs for the purposes of this study. Inpatient admission does not include admissions to rehabilitation facilities, hospice facilities, skilled nursing facilities, nursing homes, routine emergency room admissions, same day surgery (as outpatient/same day/ambulatory procedures) or social admission (e.g., subject has no place to sleep).

6.7.6 Reporting Procedures for Adverse Events

The investigator is responsible for ensuring that all grade 3 and above non-serious adverse events (as defined in Section 6.7.1 and as further specified below) observed by the investigator or reported by subjects are collected and recorded in the CRF. Source documents may include the subjects' medical records, patient diaries or study-specific worksheets. Recording for all events should be done in a concise manner using standard, acceptable medical terms.

The adverse event recorded should not be a procedure or a clinical measurement (i.e., a laboratory value or vital sign) but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement.

Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an adverse event). Further, a procedure or surgery is not an adverse event; rather, the event leading to the procedure or surgery is considered an adverse event. Any event requiring unplanned in-patient hospitalization that occurs during a subject's participation in a trial must be reported as an SAE, as previously stated.

If, in the investigator's judgment, a clinically significant worsening from baseline is observed in any laboratory or other test parameter (e.g., electrocardiogram (ECG), angiogram), physical exam finding, or vital sign, a corresponding clinical adverse event should be recorded.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the adverse event, whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an adverse event, using appropriate medical terminology (e.g., thrombocytopenia, peripheral edema, QT prolongation).

For these adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event (e.g., study drug, other illness, progressive malignancy, etc.). The relationship of the adverse event to the investigational product will be assessed by means of the question, "Is there a reasonable possibility that the event may have been caused by the investigational product?" The investigator should respond to this question with either Yes or No.

6.7.7 Reporting Procedures for Serious Adverse Event (on-site SAEs)

New SAEs will be collected and recorded throughout the study period, from the signing of the informed consent through 28 days after the final dose of study treatment. Ongoing SAE/SUSARs with a causal relationship to the investigational product will be followed until the event or its sequelae resolve or stabilize at a level acceptable to the investigator or designee.

6.7.8 Reporting to IRB

All serious adverse events that occur after the subject has signed the informed consent form or during the study at the University of Washington or Fred Hutchinson Cancer Center and meet IRB reporting criteria must be reported to the Cancer Consortium IRB (CC-IRB, fax 206-667-6831). AEs that are *unexpected, possibly related to the study drug,* and *serious or suggest a risk of greater harm from the research then previously known* will be reported to the IRB within 10 calendar days of the Investigator's awareness of the event.

The Adverse Event Reporting Form is available online:

http://extranet.fhcrc.org/EN/sections/iro/irb/forms/index.html#Reporting (as of Jan2012).

SUSARs will be reported on the Expedited Reporting Form for Unanticipated Problems or Noncompliance. Special Reporting Situations (SRS) will be reported to CC-IRB either immediately or at annual renewal, upon consultation with IRB staff. The SAE, SUSAR or SRS should be recorded on the appropriate case report form (CRF).

Reports of SAEs should be signed and dated by the principal investigator. In the absence of the PI, reports should be signed and dated by the individual reporting the event. If s/he is not medically licensed, the report should also be signed by a licensed medical practitioner, preferably a sub-investigator for this protocol. The PI will review and sign the report at the next opportunity.

Each report should contain the following information:

- Protocol number
- Subject number
- Disease/histology if applicable

Date the event occurred

- Description of the SAE
- Relationship of the event to treatment or other causality
- Whether the event was "expected'
- Severity of the event
- Intervention
- Outcome of the event
- Detailed text that includes the following information:
  - An explanation of how the SAE was handled
  - A description of the patient's condition
  - Indication whether the subject remains on study
  - Recommendation whether an amendment will need to be made to the protocol and/or the consent form.

Relevant, redacted medical records should be provided as soon as they become available; autopsy reports should be provided for deaths if available. Determination of expectedness will be based on the contents of the current Investigator's Brochure or package insert.

If a subject is permanently withdrawn from the study because of a serious adverse event, this information must be included in the End of Study Case Report Form as well as all SAE/SUSAR reports.

6.7.9 Annual Safety Reports

In addition to the expedited reporting, sponsor shall submit, once a year throughout the clinical trial or on request a safety report to the competent authority and Institutional Review Board, considering all new available safety information received during the reporting period.

6.8 Criteria for Discontinuation of Study

- The patient develops an unacceptable toxicity
- Disease progression per RECIST 1.1 criteria
- The patient develops a concurrent illness that is a contraindication to receiving further

treatment.
- The patient elects to discontinue treatment or withdraws consent.
- At the discretion of the Investigator.

6.9 Withdrawal from Study

The investigator may withdraw a patient from any phase of the study for any of the following reasons.

- Patient meets criteria for discontinuation of treatment.
- Patient receives prohibited medications. I.e., concurrent administration of other anticancer therapy, immunotherapy or investigational drug therapy given for any reason during study treatment Phase.
- Patient withdraws consent. In this event, the reason(s) for withdrawal must be documented and clarification if withdrawal of consent includes follow-up phase for progression data collection. If a subject terminates the study early, an Early Termination visit will be performed.

6.10 Data Safety Monitoring Plan

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state, and federal guidelines.

7 STUDY ACTIVITIES

7.1 Study Visit Overview

- Expected toxicities, potential risks, and dose modifications are described in Section 5 (Risks and Precautions and Dose Reductions).

- No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

7.2 Screening Period

Screening procedures to be completed within 30 days prior to the start of study treatment,

- Informed consent
- Medical history and demographics
- Concurrent illness

- Physical examination, including weight and height
- Vital signs including blood pressure, heart rate, temperature.
- Assessment of ECOG Performance Status
- Clinical laboratory tests:
  - CBC (WBC, absolute neutrophil count, hemoglobin, hematocrit, platelets)
  - Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin),
  - Serum chemistries (albumin, sodium, potassium, carbon dioxide, creatinine, BUN, glucose, calcium)
  - PSA
  - Circulating tumor cells (optional) and cell free DNA collection
- Bone scan
- CT or MRI of the abdomen/pelvis
- Chest film or chest CT if indicated

Concomitant medications listing: Obtain a complete and thorough listing of all prescription and nonprescription (over the counter) medications currently taken including pain medications.

- Obtain the sequencing report (UW Oncoplex, Foundation One, etc.) wherein BRCA1/2, ATM mutation is reported and investigator to review for suitability to study.

7.3 Treatment Period

7.3.1 Day 1

On Day 1 (± 3 days) of each cycle the following procedures will occur:

- Vital signs (blood pressure, heart rate, temperature, and weight)
- CBC (WBC with differential count, RBC, hemoglobin, hematocrit, platelets)
- Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin)
- Serum chemistries (albumin, sodium, potassium, chloride, carbon dioxide, creatinine, BUN, calcium, glucose)
- PSA will also be collected if it is clinically indicated.
- CT or MRI of the abdomen/pelvis and Chest film or chest CT will be repeated every 3 months, or as clinically indicated.
- Bone scan - if bone lesions are present at baseline, then bone scans will be performed every 3 months, at development of progression by RECIST or as clinically indicated whichever occurs first.

7.4 Termination Visit/End of Treatment

Termination visit to occur within 28 days (± 7 days) of last dose of study medication if possible. The following procedures will occur at this visit:

- Physical examination, including weight and height
- Vital signs including blood pressure, heart rate, temperature.
- Assessment of ECOG Performance Status
- Clinical laboratory tests:
  - CBC (WBC, absolute neutrophil count, hemoglobin, hematocrit, platelets)
  - Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin),
  - Serum chemistries (albumin, sodium, potassium, , carbon dioxide, creatinine, BUN, glucose, calcium)
  - PSA
  - Circulating tumor cells (optional) and cell free DNA collection

8 PLANNED STATISTICAL METHODS

8.1 Determination of Sample Size

The proportion of patients with PSA decline by 50% from baseline (PSA_{50}) will be evaluated. The primary efficacy endpoint is the percent of patients achieving PSA_{50} with docetaxel and carboplatin. The historical comparison is a PSA_{50} of 26%. The target response rate is 60%. The study will follow an optimal two-stage Simon design (Simon, 1989) where the null hypothesis that the true PSA response rate (PSA decline by 50% from baseline) is 0.26 will be tested against a one-sided alternative.

We will use a Simon minimax 2-stage design, which will allow early stopping for futility after the first stage if the response rate is low. Our null and alternative hypotheses are H0: $p \leq 26\%$ vs. H1: $p \geq 60\%$. The minimax 2-stage design for these parameters requires a first stage enrolling 5 patients. If 1 of the first 5 patients achieves a PSA_{50} response, H0 cannot be rejected. If ≥ 1 of 5 patients respond, enrollment in that cohort continues until 14 patients have completed the trial, and the response rate is calculated for all 14 patients. If ≤ 6 of 14 patients have a PSA_{50} the null hypothesis cannot be rejected. This design will provide 80% power to detect a PSA_{50} rate of 60% (one-sided $\alpha=0.05$). This design also provides a 60% probability of early stopping if H0 is true, affording protection against treating more patients than necessary if the treatment is not effective.

8.2 Analysis Populations

All patients who receive at least one dose of study drug will be included in the analysis.

8.3 Demographics and Baseline Characteristics

Demographic variables will include age, race, height, and weight. Baseline disease characteristics will include clinical stage, date of diagnosis, histology.

9 REFERENCE LIST

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10 APPENDICES

APPENDIX 1 - SCHEDULE OF EVENTS

Procedure	Screening (within 30 days prior to Day 1)[1]	Day 1 of Every Cycle[2]	Termination Visit[17]
Informed Consent	X		
Registration	X		
Medical History	X		
Physical exam	X		X
Vital Signs	X	X	X
ECOG performance status	X		X
CBC (w/ platelets, ANC)	X	X	X
Serum chemistry & electrolytes	X	X	X
Hepatic function	X	X	X
PSA	X	X***	X
CT or MRI of pelvis/abdomen	X	X**	X**
Bone scan	X	X**	X**
Chest film or chest CT	X	X**	X**
Docetaxel and carboplatin		X	
Adverse Events		X	X
Concomitant Medications	X		
Circulating tumor cells and cell free DNA collection*	X*		X*

1Baseline evaluations will be done within 30 days prior to start of therapy. With the exception of laboratory tests, which should be completed within 14 days prior to registration. All screening should be complete prior to registration.

2All study assessments and medications should be administered ±3 days of the protocol-specified date, unless otherwise noted. For patients taking Coumadin, a baseline PT/INR test should be done (further monitoring per discretion of treating physician). Hepatic function includes AST, ALT, alkaline phosphatase and total bilirubin.

17Termination visit to occur within 28 days (± 7 days) of last dose of study medication if possible.

Chemistry & electrolyte labs include: albumin, BUN, calcium, CO2, chloride, creatinine, glucose, potassium, sodium

*Circulating tumor cells and cell free DNA collection should occur one time prior to treatment and one time at progression. Circulating tumor cells are optional. If circulating tumors cells are collected for another study the results may be used.

**CT or MRI of pelvis/abdomen, bone scan, and chest film or Chest CT are done at screening, every 3 months or as clinically indicated, and at progression.

*** PSA will also be collected in the event that it is clinically indicated.

APPENDIX 2 - ADVERSE EVENTS

Definitions

Adverse Event (AE)
Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Adverse Drug Reaction (ADR)
A noxious and unintended response to any dose of the drug (or biological) product for which there is a reasonable possibility that the product causes the response. ‘‘Reasonable possibility’’ means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Serious Adverse Event (SAE)

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

- Death,
- a life-threatening adverse event,
  Life-threatening adverse event or life-threatening suspected adverse reaction.
  An adverse event or suspected adverse reaction is considered ‘‘life-threatening’’ if, in the view of the investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.
- is a suspected transmission of infectious agents by a medicinal product

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

APPENDIX 3 – PROGRESSION AND RESPONSE CRITERIA

1. Antitumor Effect– Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 criteria.

2. Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.

3. Disease Parameters

Measurable disease (Target Lesions)
Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm (this requirement based on a CT slice thickness of ≤ 5 mm; for slice thicknesses > 5 mm, measurable lesions must have a longest diameter ≥ 2 times the slice thickness).

A lymph node will be considered pathologically enlarged and measurable if its short axis is ≥ 15 mm; the short axis should be measured and followed throughout. Nodes with a short axis ≥ 10 mm and < 15 mm will be considered pathologically enlarged but nonmeasurable (see below).

Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft-tissue components will be considered measurable if the soft-tissue component can be evaluated by cross-sectional imaging (i.e., CT scan) and meets the general definition of measurability.

Simple cysts will not be considered malignant lesions and will be neither measurable nor nonmeasurable. Cystic lesions believed to be metastases may be considered measurable if they meet the general definition of measurability, but noncystic lesions are preferred as target lesions.

A lesion located in a previously irradiated area, or in an area previously subjected to any locoregional therapy, will be considered measurable only if there has been a documented increase in lesion size after prior treatment but prior to study entry.

Non-measurable disease (Non-target Lesions)
All other lesions including small lesions (longest diameter < 10 mm or pathological lymph nodes with a short axis of ≥ 10 mm and < 15 mm) and truly nonmeasurable lesions.

Lesions considered to be truly nonmeasurable include the following: bone lesions; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques. Blastic bone lesions are nonmeasurable.

4. Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

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

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

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

5. Response Criteria

Overall tumor response, as defined in Table 11, will be based on an integration of the evaluation of target, non-target, and new lesions, as described below:

5.1. Evaluation of Target Lesions

Complete Response (CR):
The disappearance of all non-nodal target lesions, with the short axes of any target lymph nodes reduced to < 10 mm.

Partial Response (PR):
At least a 30% decrease in the sum of the diameters of target lesions (including the short axes of any target lymph nodes), taking as reference the baseline sum diameter.

Stable Disease (SD):
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameter since the treatment started

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.)

Not Evaluable (NE):
A target lesion present at baseline which is subsequently not measured, or which is unable to be evaluated, leading to an inability to determine the status of that tumor for the time point in question. This category also includes scans that are not performed at this time point to evaluate the target lesion(s). The reason(s) explaining the absence of the evaluation or nonevaluable nature of the lesion(s) should be specified at the time of the assessment (e.g., early death due to malignant disease; early death due to toxicity; tumor assessments not repeated or incomplete; other [specify]).

Note: If tumor response data is missing, an overall assessment cannot be done. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

5.2. Evaluation of Non-Target Lesions

Complete Response (CR):
The disappearance of all non-target lesions, the normalization of the tumor marker level (if tumor markers are measured and are initially above the upper limit of normal, those must normalize for a patient to be considered in complete clinical response). All lymph nodes must be < 10 mm (short axis).

Incomplete Response/Stable Disease (SD):
The persistence of one or more non-target lesions and/or the maintenance of the tumor marker level above normal limits.

Progressive Disease (PD):
The appearance of one or more new lesions and/or unequivocal progression of existing non- target lesions. PD may be declared based on "unequivocal progression" in cases where the overall tumor burden increases significantly enough to require a change in therapy; in most cases, a modest increase in the size of one or more non-target lesions is not sufficient to qualify (especially in the presence of SD or PR in target disease).

Unknown (UN):
A nontarget lesion present at baseline which is subsequently not measured, or which is unable to be evaluated, leading to an inability to determine the status of that tumor for the time point in question.

This category also includes scans that are not performed at this time point to evaluate the nontarget lesion(s). The reason(s) explaining the absence of the evaluation or nonevaluable nature of the lesion(s) should be specified at the time of the assessment (e.g., early death, malignant disease; early death, toxicity; tumor assessments not repeated or incomplete; other.)

Note: Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail, and the progression status should be confirmed later by review of the Principal Investigator (or Protocol Chair). Additionally, the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is mandatory to differentiate between stable or progressive disease status.

6. Evaluation of Best Overall Response

Each response parameter (target, non-target, and new lesions) will be reported independently at each radiologic read. The investigator will decide of overall response based on the evaluation of target, non-target, and new lesions, as shown in Table 11 and Table 12.

Table 10. Time Point Response: Patients with Target (± Non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not Evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated[a]	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[a] In general, if only a subset of lesion measurements are taken at a given assessment time point, the patient as a whole is considered not evaluable for that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response.

Abbreviations: CR = complete response; NE = nonevaluable or inevaluable; PD = progressive disease; PR = partial response; SD = stable disease

Table 11. Time Point Response: Patients with Non-target Disease Only

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

[a] Non-CR/non-PD is preferred over stable disease for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials. Thus, it is not advised to assign the category of SD when no lesions can be measured.
Abbreviations: CR = complete response; NE = nonevaluable or inevaluable; PD = progressive disease

7. Duration of Response

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

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

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

8. Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression.

APPENDIX 4 – ECOG GRADING SCALE

ECOG Performance Status Scale

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