Study Title

A Phase 2 Study of Docetaxel and Carboplatin for treatment of patients with metastatic, castration resistant prostate cancer and germline or somatic DNA repair deficiency

Study Number POPCAP1

Product Name Docetaxel and Carboplatin

MIRB 00947

Funding Agency Prostate Cancer Foundation

Principal Investigator R. Bruce Montgomery, MD

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Abstract

This is a phase II study of the combination of docetaxel and carboplatin in patients with inactivation of genes in the homologous recombination pathway, including BRCA2, BRCA1, ATM, or a signature of homologous recombination deficiency (HRD). At the VA Puget Sound only, up to 5 patients with each of the following mutations may be enrolled: ATM, CDK12, BARD!, BRIP1, CHEK1, CHEK2, RAD51C, RAD51D, MRE11, ATR, FANOM, and SOP mutations (without CHD1 loss). If 2 patients with the same mutation do not achieve a PSA50 response before enrollment completes, we will terminate enrollment for this mutation for futility and it will not be considered predictive.

Patients will be treated with docetaxel (60 mg/m2) and carboplatin (AUC 5) every 21 days until complete response, progression, unacceptable toxicity, or investigator discretion. Progression will be determined by PSA, CT chest/abdomen/pelvis and bone scan per Prostate Cancer Working Group 3 (PCWG3) criteria.

The primary endpoint for the trial will be the maximal PSA response rate on docetaxel/carboplatin. This study will employ an admissible two-stage design. We expect the response rate with docetaxel/carbolatin to be 40% and consider the treatment as futile if PSA response rate is < 20%. In the first stage, 18 patients will be accrued. If there are 4 or fewer responses in these 18 patients, the study will be terminated. If more than 4 patients respond, then stage two begins and 17 additional patients will be accrued for a total of 35 at all sites who have similar studies. We will reject the null hypothesis that the treatment is futile and consider this treatment warrants further evaluation if 10 or more responses are observed in 35 patients. Patients must complete two cycles of chemotherapy to be considered evaluable. This design provides 80% power at the 5% level if the true response rate is 40%.

We plan to treat up to 20 patients at the VA Puget Sound Health Care System, and at this site we have implemented a Pre-Screening procedure that will allow for testing of patients for both certain patterns of DNA damage. Because we anticipate a 70% genetic screening failure rate, we will need to consent up to 67 patients in order to find 20 who are eligible for treatment.

List of Abbreviations

ADR	Adverse drug reaction
ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
AR	Androgen receptor
AST	Aspartate aminotransferase (SGOT)
ATM	Ataxia Telangectasia Mutated
AUC	Area under the curve (concentration vs time)
C	Celsius
CBC	Complete blood count
CLIA	Clinical Laboratory Improvement Amendments
CR	Complete response
CRPC	Castration Resistant Prostate Cancer
ctDNA	Circulating tumor DNA
CrCl	Creatinine clearance
CPK	Creatinine phosphokinase
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group (ECOG) Performance Status
F	Fahrenheit
FDA	Food and Drug Administration
FHCRC	Fred Hutchinson Cancer Research Center
GCSF/ G-CSF	Granulocyte stimulating factor
GLP	Good Laboratory Practice
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GnRH	Gonadotropin-releasing hormone
Hct	Hematocrit
Hgb	Hemoglobin
HIPAA	Health Information Portability and Accountability Act
HR	Hazard ratio
HRD	Homologous recombination deficiency
ICF	Informed consent form
ICH	International Conference on Harmonisation
ISO	Information Security Officer
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
mCRPC	metastatic Castration Resistant Prostate Cancer
MRI	Magnetic resonance imaging
mTOR	mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute

NYHA	New York Heart Association
OS	Overall survival
PARPi	poly ADP ribose polymerase inhibitor
PCF	Prostate Cancer Foundation
PCWG3	Prostate Cancer Working Group 3
PD	Progressive disease
PFS	Progression free survival
PR	Partial response
PSA	Prostate specific antigen
PSA50	Greater than 50% PSA decline
PT	Prothrombin time
QT	Time from the start of the Q wave to the end of the T wave in the heart
RANKL	Receptor activator of nuclear factor kappa B ligand
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SAFE	Safe Access File Exchange
SCCA	Seattle Cancer Care Alliance
SU2C	Stand Up to Cancer
SD	Stable disease
SOC	System Organ Class
SRS	Special reporting situations
SUSAR	Suspected unexpected adverse event reporting
ULN	Upper limit of normal
UW	University of Washington
UWMC	University of Washington Medical Center
VAMC	Veterans Administration Medical Center
VHA	Veterans Health Administration
VIReC	Veterans Administration Information Resource Center
WBC	White blood cell (count)

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1.0 Study Personnel

NAME	PAGER	EMAIL	AFFILIATION	EMPLOYEE
PI: Bruce Montgomery, MD	206-559-5058	Robert.Montgomery@med.va.gov	VA Puget Sound HCS, UW, SCCA	Attending Physician
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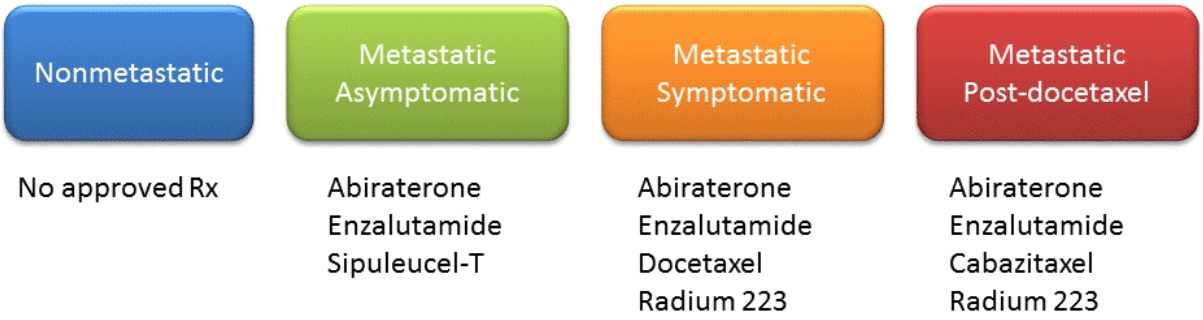
Ajjai Alva, MD	(734) 845-5800	Ajjai.Alva@va.gov	VA Ann Arbor Healthcare System	Attending Physician

2.0 Introduction

2.1 Therapy for metastatic, castration resistant prostate cancer (mCRPC)

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 mCRPC include: docetaxel (Taxotere), the androgen receptor (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 mCRPC. 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 the vast majority of patients receive either abiraterone or enzalutamide, and often radium 223, prior to docetaxel in the mCRPC setting. The second generation AR-targeting agents abiraterone and enzalutamide are FDA-approved prior to

docetaxel in patients with mCRPC. 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 PSA50 was 45-50%, PFS 6 months and median OS of 18-19 months.[2,3]

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

2.2 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.[4] 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, PSA50 25%) [5]. 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 [6]. 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 [5]. In patients with tumors refractory to docetaxel, the addition of carboplatin has been reported to result in a PSA50 rate of 18% and PFS of 3 months [7]. 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					
Regimen	**Indication**	**PSA50**	**PFS**	**OS**	**Reference**
Docetaxel/carboplatin	mCRPC 2nd line	18%	3 mos	12 mos	Ross
Docetaxel/EMP carboplatin	mCRPC 1st line	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 in particular those with mutations in homologous recombination genes such as components of the BRCA1/2-Fanconi anemia pathway 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 [8,9].

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 hypothesize that this is a subset of patients with defects in homologous recombination DNA damage repair pathway genes.

2.3 BRCA2 and DNA damage repair pathway genes in mCRPC

Recent efforts have been underway to perform molecular profiling of metastatic, castration resistant prostate cancer as part of the SU2C Prostate Dream Team research studies in an attempt to better characterize the molecular subtypes of mCRPC. Indeed, current analyses have revealed approximately 33% of CRPC metastatic tumors contain biallelic inactivation of BRCA1, BRCA2 or ATM[10]. 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 somatic biallelic inactivation. The majority of mutations identified, both in the germline deleterious variants and purely somatic loss are in the BRCA2 gene, but mutations have also been identified in BRCA1, ATM, CHEK2, RAD51D, and PALB2 (BRCA1/2-Fanconi anemia pathway genes)[10-12]. Thus, the 20-30% 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, satraplatin and mitoxantrone in the earlier studies of unselected patients with mCRPC described above.

The frequency of pathogenic germline variants in patients with mCRPC represents a significant enrichment compared to the frequency of germline DNA repair variants, generally estimated at 1-2%[12-14]. The increased frequency in germline pathogenic variants in patients with advanced disease likely results from the aggressiveness of these tumors[15,16]. The relevance of identifying germline carriers of these genes among men with advanced prostate cancer is that essentially all of the primary and metastatic tumors from these patients contain biallelic inactivation of the DNA

repair gene of interest, and these are therefore considered founder mutations and present in essentially all malignant cells [11], and Montgomery unpublished. This is similar to findings in breast cancers, which develop in women with deleterious germline BRCA1 and BRCA2 variants, in whom essentially all tumors have loss of heterozygosity of the other allele [17,18]. Hence, in the vast majority of tumors, both breast and prostate cancer develop in germline carriers harbor biallelic inactivation for the gene of interest.

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

We have identified three patients from UW/SCCA whose 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/m2 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 (PSA50).

In summary, 3 of 3 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[19]. Our experience and the literature in malignancies other than prostate cancer suggest 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. The combination of taxane with platinum is proposed as the intervention based on several factors. First, docetaxel has been shown to be effective against adenocarcinoma of the prostate and is a standard of care intervention. Second, in phase II studies the combination of docetaxel and carboplatin is at least equally as effective as docetaxel against mCRPC which is not stratified by DNA repair deficiency. Third, the experience in the treatment of serous ovarian cancers, in which 50% of patients’ tumors have inactivation of DNA repair genes demonstrates superiority of taxane plus platinum over either agent alone.

2.4.1 Additional mutation cohorts

In order to improve recruitment and keep up with the latest research in precision oncology research, we will allow up to 5 patients with ATM, CDK12, BARD!, BRIP1, CHEK1, CHEK2, RAD51C, RAD51D, MRE11, ATR, FANOM, and SOP mutations (without CHD1 loss) each. If 2 patients do not achieve a PSA50 response before enrollment completes, we will terminate enrollment for this alteration for futility and this aberration will not be considered predictive.

2.5 Response to DNA damaging agents in tumors with a signature of homologous recombination deficiency in the absence of a mutation in a DNA repair gene (VA Puget Sound only)

It has been observed in breast and ovarian cancer that some tumors which do not contain obvious mutations in DNA repair pathway genes respond exceptionally well to platinum or PARPi. Analysis of gene expression and patterns of DNA instability have revealed that many of these tumors contain a pattern of DNA damage which resembles tumors which contain a BRCA gene mutation or alteration [19,20]. This may occur through methylation of promotors for BRCA1 or BRCA2 and subsequent decrease in expression or through alterations of other genes in the DNA repair pathway [21,22]. In breast and ovarian cancer the use of signatures measuring the "BRCAness" phenotype (more accurately termed "BRCAlessness") can find patients both with and without a BRCA alteration [23] and predict responses to platinum agents and PARPi [24-26]. Sensitivity to platinum and PARPi occurs in a subset of patients with prostate cancer whose tumors do not contain BRCA mutations.

In an ongoing study of docetaxel and carboplatin with the mTOR inhibitor sirolimus at UWMC and SCCA (NCT02565901), we have treated 17 patients with docetaxel refractory metastatic prostate cancers. In that cohort, 4 patients have remained on therapy for over 40 weeks, 2 for over 70 weeks and 1 ongoing at over 90 weeks (predicted time to progression based on prior studies is 9 weeks). These patients have had targeted next generation sequencing performed on their metastatic tumors and none have alterations of any genes known to regulate DNA repair. We have also performed analysis of the metastasis biopsy DNA from patients who underwent sequencing as a component of the SU2C/PCF study which defined the current landscape of metastatic prostate cancer (Robinson). In this analysis, 423 of the total of 650 metastasis biopsies could be assessed for the presence of a signature for BRCAness. There were 61 Homologous Recombination Deficiency signature positive tumors which did not contain an alteration in any known DNA repair gene, which represents 14% of all patients who had assessable tumor (De Sarkar and Nelson unpublished). The signature analysis suggests that the largest metastasis biopsy cohort ever assembled in prostate cancer demonstrates a substantial subset of patients whose cancers do not contain a DNA repair mutation or loss (such as BRCA) but whose cancers are predicted to respond to platinum or PARPi. As a component of the current study we will test the hypothesis that a BRCAness signature (as assessed by the CLIA level assay Oncoplex) will predict for response to carboplatin based chemotherapy in men with mCRPC.

In this study we propose to prospectively assess response to the combination of docetaxel and carboplatin in patients with mCRPC who have 1) germline pathogenic variant homologous

recombination genes 2) tumors which contain biallelic inactivation of *BRCA1, BRCA2, ATM, PALB2* and *RAD51D* or other genes involved in homologous recombination, or 3) tumors which contain a signature for homologous recombination deficiency and have progressed after any succession of front-line agents.

Patients will be identified through any of the following;

1) Germline sequencing, and/or
2) Tumor sequencing using a CLIA level assay (e.g. Foundation One, Oncoplex).
3) Tumor sequencing for HRD signature using the CLIA level assay Oncoplex (HRD signature will only be performed using Oncoplex).

The focus of the study is to determine if prostate cancers that contain DNA repair deficiency through germline or other mechanisms of inactivation are sensitive to DNA damaging agents. Although the biology clearly predicts that this will be the case, the sum of the data to support activity of platinum agents in DNA repair deficient tumors comes from the single case report cited previously. In addition, in order to justify future standard of care germline screening of the population of men with metastatic prostate cancer, there must be a readily available therapeutic intervention which has been shown to be effective in deficient tumors. Even a small study evaluating response of DNA repair deficient prostate cancer could have significant implications for screening and for future studies assessing the efficacy of platinum vs. more expensive agents such as PARP inhibitors. Such a study would also justify additional efforts to improve outcomes for this subgroup of patients including chemotherapy followed by maintenance therapy with PARP inhibitors, more intensive regimens of DNA damaging agents (anthracyclines with platinum) and/or platinum based therapy at initiation of ADT for men with de novo metastatic prostate cancer.

VA Puget Sound patients who have metastatic prostate cancer and tissue that can be sequenced but do not have qualifying mutations may sign a Pre-Screening consent form so that the tissue may be sent for HRD signature analysis. *See section 5.5.2 for details.*

2.6 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.

2.6.1 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%)

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.

2.6.2 Dosing

Please refer to the docetaxel and carboplatin package inserts for complete preparation and administration. Dosing will be administered per institutional protocol. The starting doses for the study medications are as follows:

- Docetaxel 60 mg/m2 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.

2.6.3 Supply, Packaging and Storage

Docetaxel and carboplatin are stored, prepared, and administered per institutional protocol.

2.6.4 Dose Modifications

2.6.4.1 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 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 10^9/L, resume docetaxel and carboplatin at 100% of starting dose.
At any time during a cycle	
Grade 3 febrile neutropenia (defined as an ANC <1.0 x 10^9 cells/L) and a single Temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour)	Delay treatment until improvement of symptoms and resolution of the ANC to ≥1.5 x10^9 cells /L and platelet count to ≥100 x 10^9 /L.
Documented infection with Grade 3 neutropenia (defined as an ANC <1.0 x 10^9 cells/L)	Decrease BOTH docetaxel and carboplatin to 80% of starting dose for all subsequent cycles.

Grade 4 neutropenia (defined as an ANC <0.5 x 10^9 cells/L lasting more than 5 days)	With recurrence of any of these toxicities, consider removal from chemotherapy or addition of growth factor support

2.6.4.2 Dose Modifications for Hepatic Toxicity

AST/ALT > 2 x ULN OR AP > 2x ULN (unless due to bone disease) OR bilirubin > WNL	Delay treatment until recovery

2.6.4.3 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.

2.6.4.4 Dose modifications for docetaxel or carboplatin toxicity

For patients who respond to combined study treatment of docetaxel and carboplatin (by PSA and/or radiographically assessed stable disease, partial response or complete response at first restaging in 3 months) treatment will continue until disease progression or unacceptable toxicities. If there is clinical response and toxicity (such as fatigue or neuropathy), doses of either docetaxel and/or carboplatin may be reduced (up to 25%) and/or held (up to 8 weeks) per investigator discretion to improve tolerability and allow the patient to continue treatment.

For patients who respond to combined study treatment of docetaxel and carboplatin (by PSA and/or radiographically assessed stable disease, partial response or complete response at first restaging in 3 months), the docetaxel may be discontinued in the event of limiting toxicities from docetaxel and 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) per investigator discretion to improve tolerability and allow the patient to continue treatment.

2.6.4.5 Rationale for study design

The combination of docetaxel and carboplatin has activity as first and second line therapy for patients with CRPC. In the 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 in this study.

2.7. Concomitant and supportive therapies

2.7.1 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.

2.7.2 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[27].

2.7.3 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. Ongoing castration with GnRH analogue or surgical castration is required. Ongoing use of bone targeting agents (e.g. bisphosphonates, RANKL inhibitor) is allowed if initiated >4 weeks prior to initiation of study treatment. No other systemic antineoplastic is allowed. Palliative radiation to a single site is allowed at the discretion of the investigators.

2.7.4 Restrictions

The concurrent administration of other anticancer therapy, including cytotoxic or immunotherapy, is prohibited. 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.

3.0 Objectives

3.1 Primary Objective

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

3.2 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 patients with germline or somatic alterations of DNA repair pathway genes (such as BRCA1, BRCA2, ATM) or with a signature of homologous recombination deficiency
- To correlate the presence of DNA repair pathway mutations and copy number alterations in cell free DNA

4.0 Resources and Personnel

Name	Role	PHI	Recruit	Procedures	ICF	Analysis
Bruce Montgomery, MD*	PI	Yes	Yes	Yes	Yes	Yes
Matthew Rettig, MD	PI LA	No	No	No	No	Yes
Ajjai Alva, MD	PI Ann Arbor	No	No	No	No	Yes

* *Please see Study Staff Page for all other study personnel.*

Dr. Montgomery will be running this study and recruiting patients from the VA Puget Sound Health Care System. Dr Matthew Rettig has a similar study at the VA Greater Los Angeles Health Care System, and Dr. Alva has a variation of this study at the VA Ann Arbor Health Care System. None of the other sites will be performing analysis based on signatures of homologous recombination deficiency. The PIs will analyze a combined subset of data from all sites. This subset of data shared between sites will consist of the minimum data necessary to accomplish study goals. All studies will be run independently aside from data sharing.

5.0 Study Procedures

5.1 Study Design

This is an open-label study with a single phase II component.

Patients will remain on treatment until any of the following occur:

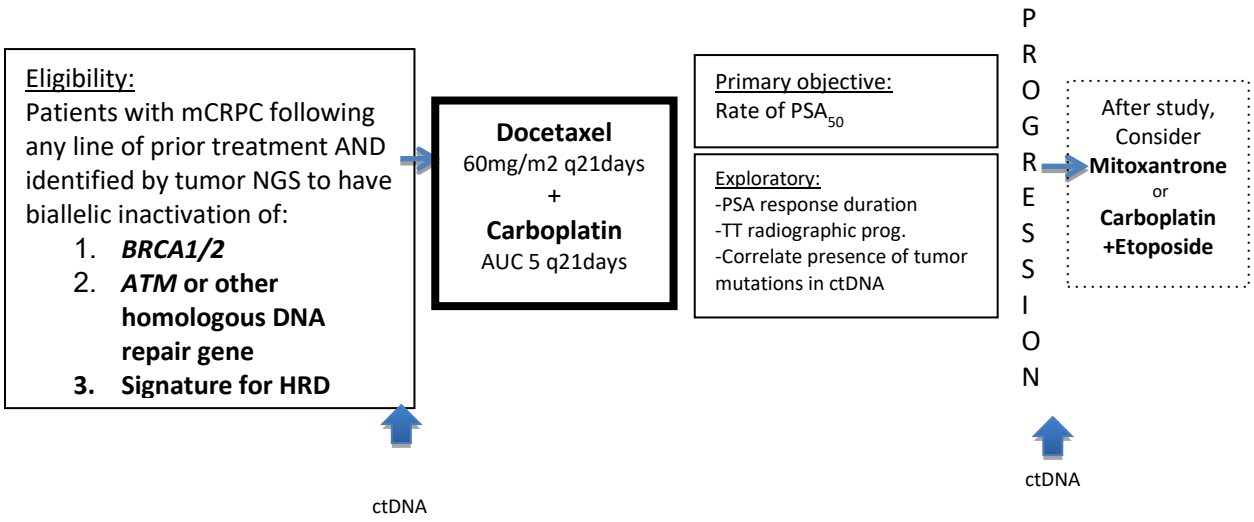
- unacceptable toxicity
- documented progression by radiographic imaging
- completion of 10 cycles of therapy (Note: Additional cycles permitted at the investigator's discretion if patients are responding and there is no evidence of cardiomyopathy or other toxicities).
- achievement of complete response (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 cycles (9 weeks), or as clinically indicated.

Bone Scan: Baseline bone scan will be performed during screening and every 3 cycles (9 weeks), or as clinically indicated.

5.1.2 Genitourinary Repository (VA Puget Sound only)

All subjects will be invited to consent to the Genitourinary Repository (MIRB 00757) at the time of consenting to this study. Cell Free DNA will only be collected from subjects who consent to the Repository because all blood samples will be stored in the Repository. Repository subjects will also be invited to donate pre and post treatment biopsies of metastatic lesions if any are amenable to the procedure, but biopsies are optional. Banked data, blood, and tissue will be stored indefinitely per the repository guidelines.



5.2 Recruitment Methods

Study subjects will be recruited from the VA Puget Sound Health Care System, the VA Ann Arbor, and the VA Greater Los Angeles Health Care System.

At the VA Puget Sound, eligible patients will be identified during routine review of the urology/oncology clinic. Their providers will give a brief introduction to the study, and if the patients are interested, they will be referred to the Investigators or study coordinator for a more detailed discussion and consenting. When presenting a research study to a patient the investigator will present multiple care options when it comes to research studies (these options are also described within the 'alternatives to participation' section of the consent form). The physician will discuss benefits and risks of each of the patients' options (research and non-research). The patient will then determine which of these care options they are interested in. This also prevents undue coercion because the provider is discussing all available options with the patient for their cancer care with no emphasis being placed on which option the patient should choose. No subject will be coerced in any way during the consenting process or during the study. Patients will be informed that participation in research studies is voluntary. Subjects will be informed that they do not need to participate in the study, that the subject can change their mind and decide to or not to participate at any time without penalty or loss of benefit to which they are otherwise entitled, and that the choice to participate or not participate in the study will not affect their VA care. Subjects can take the consent form home to discuss with their family, friends, or another doctor such as their primary care physician, and may return whenever they like to sign it or further discuss the study.

A total of 18-35 subjects will be enrolled in the study, up to 20 of whom will be enrolled at the VA Puget Sound. Due to the anticipated pre-screening failure rate, we anticipate consenting up to 67 patients in order to find 20 who qualify for treatment. This study will not use any advertising materials. Subjects will not be paid.

5.3 Informed Consent Procedures

Study personnel who have been delegated to obtain informed consent will approach interested subjects during their clinic visit and will give them a brief verbal overview of the study. Those who are interested will be taken to a private room with their companions (if they wish), and the study personnel will review the whole ICF with them, answering any questions or concerns that may arise. Once all questions have been answered, the subject will sign the ICF and HIPAA under the supervision of the study personnel, who will also sign. Subjects may also take the ICF home for discussion with their physician or significant others, but must return to the VA Puget Sound to review, ask questions, and sign the ICF and HIPAA in the presence of qualified study personnel prior to any study-related procedures.

We will be requesting a waiver of informed consent and HIPAA for screening so that we can identify eligible subjects when we review the lists of patients coming into the genitourinary oncology clinic. Written informed consent will be obtained from all subjects prior to any study procedures by study personnel (investigators and coordinators) who have been trained in the VA human subjects protections requirements and in the process of obtaining and documenting informed consent. All current study personnel have extensive experience obtaining and documenting informed consent. Any new study personnel who have not had such experience will be trained in several stages, including verbal instruction, shadowing consenting visits, VA training modules, and observation by qualified personnel.

Consent will be documented by the signed Informed Consent Form (ICF) and by a Research Screening/Enrollment Note in the patient's medical record. A copy of the signed form will be provided to the subject. No study procedures will be performed until after the ICF and HIPAA have been signed. All subjects must be able to give consent without the help of a legally authorized representative, and those with impaired decision-making capability or those who cannot read will not be included on this study.

Study personnel obtaining informed consent will check that:

- The most recent ICF and HIPAA forms are being used
- All pages have the IRB approval stamp
- All pages are present
- Names, signatures, and dates are correct and none have been missed
- Any errors have been properly corrected with one line through them and an initial and date
- A copy of the signed ICF and HIPAA is given to the subject
- An enrollment note is present in the patient's medical record or as a hard copy
- A copy of the ICF has been sent to the RCO within 3 days

5.4 Inclusion/Exclusion 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 > 18 years

3. Known prostate cancer

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 < 50ng/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 (Response Evaluation Criteria in Solid Tumors).

    - Progression of metastatic bone disease on bone scan with > 2 new lesions.

6. Prior therapy with abiraterone acetate, enzalutamide, 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 $\leqslant$ 2.

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 initiating therapy:

    - Absolute neutrophil count >1.5 x 109 cells/L

    - Hgb > 9.0 g/dL

    - Platelets >100,000 x 109/L

    - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin levels < 1.5 x ULN

12. Presence of inactivation of BRCA1, BRCA2, or ATM genes OR one of the following:

- Patients with clearly deleterious mutations of other genes involved in homologous DNA repair may be included at the investigator's discretion.
- Patients with homozygous inactivation of genes involved in homologous recombination from primary or metastatic tumor as assessed by a CLIA level assay for DNA sequencing may be included.
- Patients with a signature of homologous recombination deficiency ("BRCAness") in primary or metastatic tissue may be included (VA Puget Sound only).

Up to 5 patients with each of the following mutations may be enrolled: ATM, CDK12, BARD!, BRIP1, CHEK1, CHEK2, RAD51C, RAD51D, MRE11, ATR, FANOM, and SOP mutations (without CHD1 loss). If 2 patients with the same mutation do not achieve a PSA50 response before enrollment completes, we will terminate enrollment for this mutation for futility and it will not be considered predictive (VA Puget Sound only).

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 small cell carcinoma (morphology alone – immunohistochemical evidence of neuroendocrine differentiation without morphologic evidence is not exclusionary).
3. Prior treatment with platinum-based chemotherapy for prostate cancer.
4. Known parenchymal brain metastasis.
5. Active or symptomatic viral hepatitis or chronic liver disease.
6. 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.
7. Treatment with an investigational therapeutic within 30 days of Cycle 1.
8. Patients with dementia/psychiatric illness/social situations limiting compliance with study requirements or understanding and/or giving of informed consent are not eligible
9. 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.

5.5 Study Evaluations

5.5.1 Study Visit Overview

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy. See Appendix 1 for Schedule of Events.

Medical History

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

Physical Examination

Physical examination includes HEENT (head, eyes, ears, nose, and throat), chest, cardiac, abdominal, extremities, neurologic, and lymph node examinations.

Vital Signs

Vital signs include blood pressure, heart rate and temperature on day of treatment. Weight will be recorded at every chemotherapy visit. Height will be recorded at initial clinic visit only.

Imaging

CT or MRI of the abdomen/pelvis will be performed during screening and every 3 cycles (9 weeks), or as clinically indicated. A chest film or chest CT will be performed if clinically indicated.

Bone Scan: Baseline bone scan will be performed during screening and every 3 cycles (9 weeks), or as clinically indicated.

Clinical Safety Laboratory Tests

Clinical safety laboratory tests will be assessed as VA 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.

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: • Blood urea nitrogen (BUN) • Carbon dioxide (CO_2) • Chloride (Cl) • Creatinine • Glucose • Potassium (K) • Sodium (Na) *Additional laboratory tests: Add Prothrombin Time (PT/INR) test per institutional guidelines for patients who are taking Coumadin while on study.

Research Labs
Please refer to the laboratory manual for details.

Sample Collection, Storage, and Shipping
The relevant VAMC 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

5.5.2 Pre-Screening Period (VA Puget Sound only)
Patients who have metastatic prostate cancer but do not have previous tests that confirm the presence of qualifying DNA mutations may sign a Pre-Screening consent form giving the study team permission to send blood or archival tumor tissue for CLIA level assay for genetic mutations and/or signature analysis to determine whether the patient has a hallmark of DNA repair deficiency ("BRCAness" or “genomic scarring”). The archival tumor sample may come from either clinically archived samples or from samples stored in the Genitourinary Repository (MIRB 00757) if available. The samples will be analyzed using the Oncoplex assay (UW CLIA certified assay) for the presence of a signature of homologous recombination deficiency.

Patients whose pre-screening genetic tests are positive for genomic scarring will be invited to sign the Main Study Consent Form and enter the Screening Period. Patients who already have results showing that they have qualifying mutations do not need to complete Pre-Screening. They will sign the Main Study Consent Form and enter Screening directly.

5.5.3 Screening Period
Screening procedures to be completed within 30 days prior to the start of study treatment for patients who have qualifying mutations or DNA damage patterns. Baseline 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 initiating therapy. All screening should be complete prior to initiating therapy.

- 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
- Blood collection within 14 days prior to initiating therapy for:
    - CBC (WBC with differential count, RBC, hemoglobin, hematocrit, platelets)
    - Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin),
    - Serum chemistries (sodium, potassium, chloride, carbon dioxide, creatinine, BUN, glucose)
    - Add prothrombin time (PT/INR) per institutional guidelines for patients who are taking coumadin while on study
    - PSA
    - Cell free DNA blood sample
- Bone scan

- CT or MRI of the abdomen/pelvis
- Chest film or chest CT if indicated
- Concomitant medications. 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 or HRD signature is reported and investigator to review for suitability to study. Patients who do not already have qualifying sequencing results must complete Pre-Screening first.

5.5.4 Treatment Period

Day 1

Study assessments and medications should be administered ±4 days of the protocol-specified date, unless otherwise noted. Cycles are 21 days long.

On Day 1 (± 4 days) of each cycle the following procedures will occur:

- Vital signs (blood pressure, heart rate, temperature and weight)
- Review adverse events and changes in concomitant medications
- Blood collection for:
    - CBC (WBC with differential count, RBC, hemoglobin, hematocrit, platelets)
    - Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin)
    - Serum chemistries (sodium, potassium, chloride, carbon dioxide, creatinine, BUN, glucose)
    - Add prothrombin time (PT/INR) per institutional guidelines for patients who are taking coumadin while on study
    - Cell free DNA collection
- Treatment with docetaxel & carboplatin

- 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.

5.5.5 Study Discontinuation Visit

This visit should occur within 28 days (± 7 days) of last dose of study medication if possible.

- Physical exam
- Vital Signs
- ECOG performance status
- Blood collection for:
    - CBC (WBC with differential count, RBC, hemoglobin, hematocrit, platelets)
    - Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin)
    - Serum chemistries (sodium, potassium, chloride, carbon dioxide, creatinine, BUN, glucose)
    - Add prothrombin time (PT/INR) per institutional guidelines for patients who are taking coumadin while on study

    - PSA
    - Cell free DNA collection
- Adverse Events

5.6 Data Analysis

Criteria for Evaluation

Antitumor effects:

- The percentage of patients achieving ≥50% reduction in PSA according to PCWG3 criteria
- The percentage of patients achieving ≥90% reduction in PSA according to the PCWG3 criteria
- The percentage of patients achieving ≥30% reduction in measurable disease by RECIST.
- Median time to tumor progression by PCWG3 criteria

Statistical Methods:
This is a phase II open-label, single-arm study in patients with mCRPC who have progressed on abiraterone acetate, enzalutamide, or docetaxel. Patients will be treated docetaxel/carboplatin every three weeks concomitant maintenance of castrate levels of serum testosterone by GnRH analogue or surgical castration. Therapy will continue until disease progression, unacceptable toxicity, complete response, or patient withdraws consent.

The primary endpoint for the trial will be the maximal PSA response rate or docetaxel/ carboplatin. Patients must complete two cycles of chemotherapy to be considered evaluable. This study will employ an admissible two-stage design. We expect the response rate with docetaxel/carboplatin to be 40% and consider the treatment as futile if PSA response rate is < 20%. In the first stage, 18 patients will be accrued. If there are 4 or fewer responses in these 18 patients, the study will be terminated. If more than 4 patients respond, then stage two begins and 17 additional patients will be accrued for a total of 35. We will reject the null hypothesis that the treatment is futile and consider this treatment warrants further evaluation if 10 or more responses are observed in 35 patients. This design provides 80% power at the 5% level if the true response rate is 40%.

Study Endpoints:
ctDNA will be collected as per standard operating protocol (appendix).

5.6.1 PLANNED STATISTICAL METHODS

Determination of Sample Size

The primary endpoint for the trial will be the maximal PSA response rate on docetaxel/carboplatin. This study will employ an admissible two-stage design. We expect the response rate with docetaxel/carbolatin to be 40% and consider the treatment as

futile if PSA response rate is < 20%. In the first stage, 18 patients will be accrued. If there are 4 or fewer responses in these 18 patients, the study will be terminated. If more than 4 patients respond, then stage two begins and 17 additional patients will be accrued for a total of 35. We will reject the null hypothesis that the treatment is futile and consider this treatment warrants further evaluation if 10 or more responses are observed in 35 patients. Patients must complete two cycles of chemotherapy to be considered evaluable; we expect a 5% drop out rate, so we plan to enroll 35 patients in total. This design provides 80% power at the 5% level if the true response rate is 40%.

The Investigators at all sites will analyze the limited data sets from all sites after phase 1 and at the end of the study.

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

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

5.7 Withdrawal of Subjects

Criteria for Discontinuation of Study

- The patient develops an unacceptable toxicity
- Radiographic disease progression per RECIST 1.1 or PCWG3 criteria
- Clinical disease progression as assessed by the investigator
- 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.

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

5.8 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 reported according to the following sections.

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

6.0 6.0 Reporting

6.1 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 study medication) 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. 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

6.2 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 notify the IRB, and FDA according to site reporting policies (see section 6.4).

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

6.3 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;
    - 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).

6.4 Reporting Procedures for Adverse Events

The investigator is responsible for ensuring that adverse events observed by the investigator or reported by subjects are collected and recorded in the CRF. All unexpected observed or volunteered adverse events will be recorded on the adverse event page(s) of the case report form (CRF) throughout the study period, from the signing of the informed consent through 28 days after the final dose of study treatment.

All AEs that are related to the study medication (listed in the prescribing information for the study drugs) of CTCAE v4.0 grade 3 or 4 will be recorded and reported per VA guidelines, but non-serious AEs grade $\leqslant$ 2 that are expected and related to the study medication will only be recorded if the Investigator determines that they are clinically significant. 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 the course of 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 all 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.

6.4.1 Serious Adverse Events (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.

6.4.2 Reporting to IRB

AEs, SAEs, deviations, and problems should be reported per VA and local regulations. The requirements for the VA Puget Sound are listed here.

Local research deaths that are <u>both unanticipated and related to research</u> must be reported orally to the HRPP director immediately. Written notification must be sent within 5 business days.

Local SAES/Serious problems that are <u>both unanticipated and related to research</u> must be reported in writing to the IRB within 5 days.

Events/problems that do not meet immediate reporting criteria should be reported to the IRB at the time of continuing review.

6.4.3 Medical Monitor

Dr. Wu, Chief of Oncology at the VA Puget Sound HCS will review safety and toxicity data (if any) for subjects at all sites every 6 months, or as necessary.

7.0 Privacy and Confidentiality

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the study objectives. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Study personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IRB review, and regulatory inspection. The consent also addresses the transfer of the data to other entities.

The subject has the right to request through the investigator access to his personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

All study personnel will be trained in GCPs, HIPAA, and research regulations. Data will be stored in secure databases, on secure servers, or in locked cabinets in locked offices.

8.0 Communication Plan

The site investigators at VA Puget Sound, VA Ann Arbor, and VA West Los Angeles will monitor study progress at both sites, including response and toxicities through regular teleconferences and email communication. The toxicities of docetaxel and carboplatin have been described in multiple phase I/II studies, and grade 3 or 4 toxicities are rare as per protocol. Because the drugs are being administered per standard of care and the toxicity profile has been described, it is felt that detailed toxicity monitoring is not critical. Monthly teleconferences are already in place between the sites and the sponsor, Prostate Cancer Foundation, to monitor study performance as a whole and this will continue for duration of study. During this call investigators will communicate unexpected toxicities at each site and determine cumulative toxicity across the study.

9.0 Information Security and Data Storage/Movement

After consenting, data regarding the patient's medical history and cancer treatment will be collected from patients and from CPRS. It will be stored on paper and electronically. Paper PHI will be stored together with study data in charts kept in locked cabinets in locked offices belonging to study personnel. Electronic data will be stored on secure VA servers accessible only to study personnel through secure, password-protected VA computers or VA web portals. All personnel who have access to study data agree to keep it confidential, and site personnel have all been trained in VA privacy policies. The Master Patient List will be kept separate from

study data. All study personnel will abide by GCPs, the HIPAA privacy law, and all other applicable laws and regulations.

Data necessary for analysis of study results will be shared with researchers at other VAs who are affiliated with this study for analysis via secure portal (VA's VIReC RedCap system), secure fax, tracked mail, email, Safe Access File Exchange (SAFE), Virtru, or other method approved by the ISSO.

Study data will be archived and destroyed per VHA records control requirements.

Some genomic and medical data may be shared with NIH databases such as the National Institutes of Health (NIH) Genomic Data Repository, GenBank, and National Cancer Foundation (NCF). The data will not contain any names, addresses, or personally identifiable information that could be used to identify individuals. These databases are available to help researchers understand different diseases. These databases contain DNA code and medical information from participants who have various diseases.

As part of this study, we may release DNA and disease information about our patients into relevant genetic databases in order to help researchers understand the relationship between DNA and diseases.

The DNA code in a genetic database cannot be used by itself to identify any specific person. A researcher who already has DNA code for one person could use information from a genetic database to learn more about that person. Once we release information to a genetic database, we no longer have any control over the use of this information

10.0 References

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11.0 Appendices

Appendix 1: Schedule of events

Procedure	Pre-Screening[8]	Screening (within 30 days prior to Day 1)[1]	Day 1 of Every Cycle[2]	Termination visit[5]
Informed Consent	X (Pre-Screen)	X (Main)		
Medical History		X		
Physical exam		X		X
Vital Signs		X	X	X
ECOG performance status		X		X
CBC (w/ platelets & differentials)		X	X	X
Serum chemistry & electrolytes[3]		X	X	X
Hepatic function[4]		X	X	X
PSA		X		X
CT or MRI of pelvis/abdomen[6]		X		
Bone scan[7]		X		
Chest film or chest CT[6]		X		
Docetaxel and carboplatin			X	
Adverse Events			X	X
Concomitant Medications		X	X	
Cell free DNA collection		X	X	X
DNA sequencing for signature analysis	X[8]			

1. Baseline 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 initiating therapy. All screening should be complete prior to initiating therapy.
2. All study assessments and medications should be administered ±4 days of the protocol-specified date, unless otherwise noted. Cycles are 21 days long.
3. Chemistry & electrolyte labs include: BUN, CO2, chloride, creatinine, glucose, potassium, sodium. Add Prothrombin Time (PT/INR) test per institutional guidelines for patients who are taking Coumadin while on study.
4. Hepatic function includes AST, ALT, alkaline phosphatase and total bilirubin.
5. Termination visit to occur within 28 days (± 7 days) of last dose of study medication if possible.
6. CT or MRI of the abdomen/pelvis will be performed during screening and every 3 cycles (9 weeks), or as clinically indicated. A chest film or chest CT will be performed if clinically indicated.
7. Bone Scan: Baseline bone scan will be performed during screening and every 3 cycles (9 weeks), or as clinically indicated.
8. Pre-Screening and signature analysis only available at the VA Puget Sound. This may be performed at any time prior to Screening.

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 cause 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

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.

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.

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 subsequent to 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.

1. 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 5mm 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.

2. 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:

2.1. **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 particular 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 (eg, 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.

2.2. 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 on the basis of “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 particular 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 at a later time 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.

3. 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 make a determination 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

4. 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.

5. Progression-Free Survival

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

9. Bone Scan Progression per PCWG3

The criteria for radiographic progression by bone scan are based on the recommendations of the PCWG3. The evaluation of radiographic bone lesion response will be performed by bone scan only. Of note, progressive disease determination for bone scan disease requires a confirmatory scan as outlined below.

Prior to the Week 12 assessment, a patient will be considered to have progressed if the bone scan shows ≥ 2 new lesions compared with baseline and confirmed ≥ 6 weeks later by a second bone scan showing ≥ 2 additional new lesions (total of ≥ 4 new lesions compared with baseline).

After the Week 12 assessment, a patient will be considered to have progressed if the bone scan shows ≥ 2 new lesions compared with baseline and confirmed ≥ 6 weeks later by a second bone scan.

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.