MD Anderson IND Sponsor Cover Sheet	
Protocol ID	2015-0723
Protocol Title	A Phase II Study with a Limited Safety Lead-In of Enzalutamide in Combination with Carboplatin and Paclitaxel in Advanced Stage or Recurrent Endometrioid Endometrial Cancer
Protocol Phase	II
Protocol Version	19
Version Date	5/11/2021
Phase	II
Protocol PI	Shannon Westin, MD
Department	Gynecologic Oncology and Reproductive Medicine
IND Sponsor	MD Anderson Cancer Center
IND #	129179

NCCN Project #: NCCNENZA0017

Local Protocol #: 2015-0723

TITLE: A Phase II Study with a Limited Safety Lead-In of Enzalutamide in Combination with Carboplatin and Paclitaxel in Advanced Stage or Recurrent Endometrioid Endometrial Cancer

Coordinating Center: M. D. Anderson Cancer Center

Principal Investigator:

Shannon N. Westin, MD, MPH

Department of Gynecologic Oncology & Reproductive Medicine, Unit 1362
1155 Herman Pressler
Houston, TX 77030
713-794-4314 (office)
713-792-7586 (fax)
SWestin@mdanderson.org

Co-Principal Investigator:

Pamela T. Soliman, MD

Department of Gynecologic Oncology & Reproductive Medicine, Unit 1362
1155 Herman Pressler
Houston TX 77030
713-745-2352 (office)
713-792-7586 (fax)
psoliman@mdanderson.org

Co-Investigators:

Karen H. Lu, MD

Department of Gynecologic Oncology & Reproductive Medicine, Unit 1362
1155 Herman Pressler Blvd
Houston TX 77030
713-745-8902 (office)
KHLu@mdanderson.org

Gordon B. Mills, MD, PhD

Director of Precision Oncology - OHSU Knight Cancer Institute
Professor – Cell, Developmental & Cancer Biology
Knight Cancer Institute | Oregon Health & Science University
2730 SW Moody Ave, Portland, OR 97201
Phone: 503-346-4660
millsg@ohsu.edu

Preetha Ramalingam, MD

Department of Pathology, Unit 0085
1515 Holcombe Blvd
Houston TX 77030
713-794-5698 (office)
pramalingam@mdanderson.org

Nicole Fleming, MD

Department of Gynecologic Oncology & Reproductive Medicine, Unit 1362
1155 Herman Pressler Blvd
Houston TX 77030
281-566-1900 (office)
nfleming@mdanderson.org

Hai Tran, PHARMD

Department of Thoracic Head & Neck Medical Oncology, Unit 0432
1515 Holcombe Blvd
Houston, TX 77030713-792-9531 (office)
htran@mdanderson.org

Statisticians:

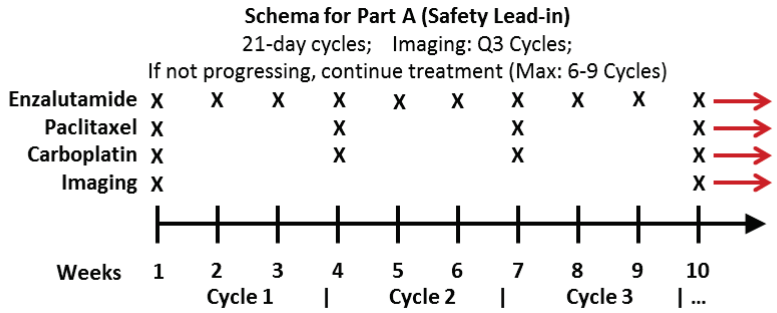
Ying Yuan, PhD

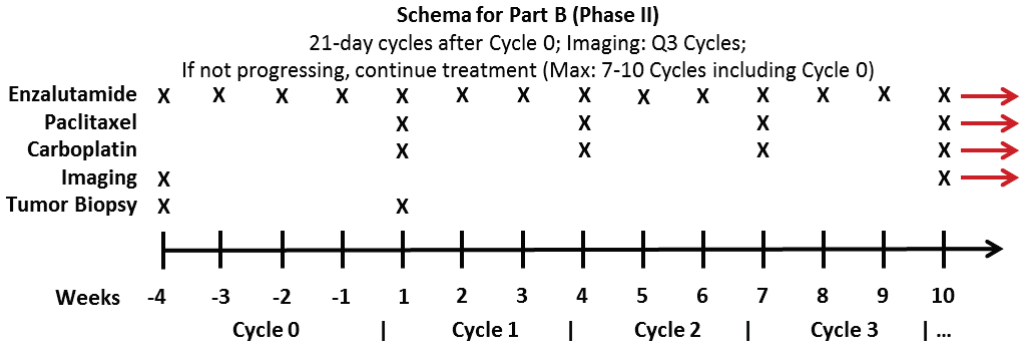
Department of Biostatistics, Unit 1411 MD Anderson Cancer Center
1400 Herman Pressler
Houston, TX 77030
Phone: 713-563-4271
yyuan@mdanderson.org

STUDY SCHEMA

Patients who have had NO prior chemotherapy for advanced stage, metastatic or recurrent endometrial cancer with measurable disease will enter either a safety lead-in or Phase II portion of the study. The Patients in the safety lead-in portion (Part A) will start at Cycle 1 and receive 6-9 cycles of combination treatments of oral, daily 160 mg enzalutamide and Paclitaxel and Carboplatin on day 1 of each cycle. Patients in the Phase II portion will start at Cycle 0 which is induction treatment with ONLY enzalutamide (160 mg daily orally) for 28 days. Once translational biopsies are obtained (day 26-28), patients will be initiated on combination therapy of enzalutamide (daily), paclitaxel (Day 1 of each cycle), and carboplatin (Day 1 of each cycle) every 21 days (Cycle 1 through Cycles 6-9).

Each study drug may be dose reduced individually. Enzalutamide dose modification may occur in light of





Enzalutamide-related toxicity when administered alone during cycle 0 for patients enrolled in Phase II (Part B) as well as when administered in combination with Paclitaxel and Carboplatin during cycle 1 and subsequent cycles for patients enrolled in the Safety Lead-in (Part A) and Phase II (Part B). Paclitaxel and Carboplatin dose modifications may not occur in cycle 1 and are only applicable to subsequent treatment cycles. Each dose reduction of Enzalutamide, Paclitaxel and/or Carboplatin will be based upon the toxicity. Please see section 5.0 for further details on how to employ the dose modifications for each drug.

Dose Levels for Safety Lead-in and Dose-reduction Schedule for Phase II

Dose Level	Enzalutamide		Dose Level	Paclitaxel		Dose Level	Carboplatin
1	160 mg PO		1	175 mg/m^2		1	AUC 5
-1	120 mg PO		-1	175 mg/m^2		-1	AUC 5
-2	80 mg PO		-2	150 mg/m^2		-2	AUC 4
-3	Off		-3	135 mg/m^2		-3	OFF

TABLE OF CONTENTS

1.0 OBJECTIVES

1.1 Primary Objectives:

1. To determine the clinical activity of combination enzalutamide, carboplatin and paclitaxel represented as:
    a) Objective tumor response (complete response (CR) + partial response (PR))
    b) The proportion of patients who survive progression-free for at least 6 months after initiating therapy
2. To quantify protein and phosphoprotein expression of androgen receptor (AR) and AR-response genes (See Section 8.0) following enzalutamide treatment in match-paired pre and post treatment tumor biopsies
3. To determine the safety and feasibility of daily enzalutamide given in combination with carboplatin and paclitaxel in women with advanced stage or recurrent endometrial cancer

1.2 Secondary Objectives

1. Determine median response duration;
2. Estimate progression free survival and overall survival;
3. Evaluate for presence of pharmacokinetic interaction between enzalutamide and paclitaxel

1.3 Exploratory Objectives

1. Correlate molecular results, including AR receptor expression and activation, to clinical endpoints
2. Identify potential agents to synergize with enzalutamide based on pathways activated after enzalutamide treatment

2.0 BACKGROUND

2.1 Enzalutamide

Please see investigator's brochure and the Enzalutamide Package Insert for full details regarding enzalutamide.

Introduction

Enzalutamide (MDV3100) is an androgen receptor (AR) signaling inhibitor that targets several steps in the AR signaling pathway. Enzalutamide competitively inhibits binding of androgens to ARs, inhibits nuclear translocation of receptors and inhibits the association of the AR with DNA, even in the setting of AR overexpression and in prostate cancer cells resistant to antiandrogens. Enzalutamide is a selective AR signaling inhibitor. Enzalutamide exerts more substantial beneficial effects than bicalutamide in nonclinical models of castration-resistant prostate cancer (CRPC)[1] and has also shown activity in nonclinical models of breast cancer. The novel mechanism of action of enzalutamide slows tumor growth and induces apoptosis via three complementary actions: 1) enzalutamide competitively inhibits binding of androgens to the AR as it has a higher affinity for the receptor than bicalutamide and is a pure receptor antagonist whereas bicalutamide has partial agonist activity; 2) enzalutamide inhibits nuclear translocation of the AR while bicalutamide enhances this effect and 3) enzalutamide inhibits binding of the AR to DNA better than bicalutamide, even in prostate cancer cells resistant to antiandrogens and

with AR overexpression. These three properties of enzalutamide impart a more complete blockade of the AR signaling pathway in the setting of AR overexpression.

Enzalutamide was approved in the United States on 31 August 2012 under the trade name XTANDI® for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have previously received docetaxel. Enzalutamide has subsequently been approved in more than 35 countries. Clinical development is ongoing for other indications. Enzalutamide, which is formulated with Labrasol® (caprylocaproyl macrogolglycerides) and filled into soft gelatin capsules containing 40 mg of the active pharmaceutical ingredient, is provided as an orally available immediate-release dosage form.

Ongoing and completed company sponsored studies assessing enzalutamide are presented in the Investigator's Brochure and the Enzalutamide package insert. The data cut-off date for the clinical studies presented is 01 January 2014, unless otherwise noted.

Preclinical Studies

Pharmacology

The primary pharmacodynamic effect of enzalutamide is inhibition of the AR signaling pathway. Enzalutamide inhibits androgen binding to the AR, AR nuclear translocation in the presence of androgen and AR:chromatin association. In multiple prostate cancer cell lines that specifically model CRPC (LNCaP/AR, VCaP, W741C LNCaP), the consequences of enzalutamide treatment include inhibition of AR-induced gene transcription, reduced cell proliferation, increased cell death by apoptosis and tumor regression. In a mouse xenograft model of CRPC using prostate cancer cells that overexpress the AR (LNCaP/AR), enzalutamide inhibits tumor growth and reduces tumor size. One of the 2 major human metabolites of enzalutamide, N-desmethyl enzalutamide, demonstrates key primary pharmacodynamics of similar potency to the parent molecule, while the second major human metabolite, a carboxylic acid metabolite, has no known pharmacodynamic effect. In humans, N-desmethyl enzalutamide circulates at approximately the same steady-state plasma concentrations as enzalutamide and is assumed to contribute to clinical effects.

Nonclinical studies have shown that enzalutamide suppresses the growth of AR-expressing breast cancer cells that also express the estrogen receptor (ER), as well as cells that do not express the ER. Enzalutamide and N-desmethyl enzalutamide bind to and antagonize the γ-aminobutyric acid (GABA)-gated chloride channel. Enzalutamide given at high doses to mice induced dose-dependent convulsions, an observation that parallels the clinical safety data showing that dose appears to be an important predictor of the risk of seizure in patients. As some molecules that antagonize the GABA-gated chloride channel are associated with convulsions, enzalutamide and N-desmethyl enzalutamide may both contribute to the convulsions that were observed in nonclinical studies. Safety pharmacology studies evaluating the central nervous, respiratory and cardiovascular systems did not identify any additional acute effects of enzalutamide at exposures relevant to the proposed human clinical dose of 160 mg/day.

Pharmacokinetics

Nonclinical studies with in vitro test systems have contributed to the understanding of enzalutamide pharmacokinetics and the potential for drug-drug interactions (DDIs). Enzalutamide has high permeability across Caco-2 monolayers. Both enzalutamide and Ndesmethyl enzalutamide are inducers and inhibitors of P-glycoprotein (P-gp). Data from a study with human cytochrome P450 (CYP) enzymes showed that CYP2C8 and CYP3A4/5 are both responsible for the metabolism of enzalutamide, and a clinical study showed that it is primarily CYP2C8 that is responsible for the metabolism of enzalutamide and the subsequent formation of the active metabolite (N-desmethyl enzalutamide). Inhibition studies with CYP enzymes showed that enzalutamide, N-desmethyl enzalutamide, and the inactive carboxylic

acid metabolite caused direct inhibition of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 and time-dependent inhibition of CYP1A2. Induction studies with CYP enzymes showed that enzalutamide caused induction of CYP2B6, CYP3A4, and uridine 5'-diphospho-glucuronosyltransferase (UGT) and that enzalutamide is not expected to induce CYP1A2 at therapeutically relevant concentrations.

Subsequent clinical studies showed that enzalutamide is an inducer of CYP2C9, CYP2C19, CYP3A4, and possibly UGTIA1, while enzalutamide has no clinically meaningful effect on CYP2C8. Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin, and there is no in vitro protein binding displacement between enzalutamide and other highly bound drugs (warfarin, ibuprofen, and salicylic acid). N-desmethyl enzalutamide is 95% bound to plasma proteins.

Toxicology

Macroscopic and microscopic findings, as well as organ weight changes related to enzalutamide administration, were observed in the prostate gland, seminal vesicles, testes and epididymides after repeat dosing in mice, rats and dogs. These changes are consistent with the primary pharmacological properties of enzalutamide and have been previously observed with non-steroidal antiandrogen compounds, such as bicalutamide. Mild and reversible hypertrophy or hyperplasia of Leydig cells in the testes was found in repeat-dose studies of enzalutamide and/or N-desmethyl enzalutamide in mice and dogs. Leydig cell hypertrophy/hyperplasia is a common finding in toxicity studies for antiandrogen compounds such as bicalutamide, flutamide and nilutamide and is related to the occurrence of Leydig cell tumors in carcinogenicity studies for these agents. The extensive clinical experience with antiandrogens has shown that Leydig cell tumors in animals do not translate to a risk for humans. Mammary gland changes were not observed in male and female dogs treated with enzalutamide for 39 weeks.

In embryo-fetal toxicity studies in mice, enzalutamide induced premature deliveries in dams and embryo-fetal deaths. Decreased fetal body weights and high incidence of external and skeletal abnormalities, such as decreased anogenital distance and cleft palate associated with absent palatine bone were also observed. Such effects are likely to be attributed to AR inhibition, as similar effects in rodents have also been found for other AR antagonists. No effects on dams or on embryo-fetal development were found in rabbits.

Clinical Studies

Pharmacokinetics

The pharmacokinetics and metabolism of enzalutamide have been evaluated in patients with CRPC, hormone-naïve prostate cancer patients, healthy male volunteers, and subjects with mild or moderate hepatic impairment. Individual doses have ranged from 30 to 600 mg.

After oral administration to patients with CRPC, the median time to reach maximum enzalutamide plasma concentrations was 1 hour, and the mean terminal half-life was 5.8 days. Enzalutamide steady state was achieved by day 28, and the accumulation ratio was 8.3-fold. At steady state, enzalutamide showed approximately dose proportional pharmacokinetics over the range of 30 to 360 mg/day. A mass balance and biotransformation study in healthy male volunteers showed that enzalutamide is primarily eliminated by hepatic metabolism. A food-effects study showed that food does not have a clinically relevant effect on the AUC of enzalutamide or N-desmethyl enzalutamide; therefore, enzalutamide can be taken with or without food. Pharmacokinetics of enzalutamide monotherapy in women appear to be the same as in men.

A hepatic impairment study showed that the composite AUC of enzalutamide plus N-desmethyl enzalutamide after single-dose enzalutamide was similar in subjects with baseline mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively) relative to subjects with normal hepatic function, and no starting dose adjustment is needed. Enzalutamide is currently being evaluated in subjects with baseline severe hepatic impairment (Child-Pugh Class C).

Based on population pharmacokinetics modeling, age, weight and renal function (creatinine clearance [CLCR] ≥ 30 mL/min) do not have clinically meaningful effects on enzalutamide exposures; therefore, no dose adjustments are indicated for these covariates. Based on pharmacokinetic data from a study in Japanese patients with prostate cancer, there were no clinically relevant differences in exposure between Japanese and white patients. Clinical data are insufficient to assess the potential effect of severe renal impairment (CLCR < 30 mL/min) and end-stage renal disease on enzalutamide pharmacokinetics.

DDI studies in prostate cancer patients showed that enzalutamide can affect exposures to other co-medications. At steady state, enzalutamide reduced the AUC of oral midazolam (CYP3A4 substrate), S-warfarin (CYP2C9 substrate) and omeprazole (CYP2C19 substrate) by 86%, 56% and 70%, respectively. Therefore, enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. Substrates of CYP3A4, CYP2C9 and CYP2C19 with a narrow therapeutic index are to be avoided, as enzalutamide may decrease plasma exposure of these drugs. If enzalutamide is coadministered with warfarin (CYP2C9 substrate), additional international normalized ratio (INR) monitoring is to be conducted.

Enzalutamide (160 mg/day) did not have a clinically relevant effect on exposure to intravenous docetaxel (CYP3A4 substrate) or oral pioglitazone (CYP2C8 substrate). DDI studies in healthy subjects showed that concomitant medications can affect exposure to enzalutamide. Coadministration of gemfibrozil (a strong CYP2C8 inhibitor) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold; therefore strong CYP2C8 inhibitors are to be avoided. If coadministration with a strong CYP2C8 inhibitor is necessary, the dose of enzalutamide is to be reduced to 80 mg once daily. Co-administration of enzalutamide with strong or moderate CYP2C8 induces (e.g. rifampin) may alter the plasma exposure of enzalutamide and should be avoided if possible. Coadministration of itraconazole (strong CYP3A4 inhibitor) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold; as this small change is not clinically meaningful, no starting dose adjustment is needed when coadministering enzalutamide with CYP3A4 inhibitors. Coadministration of enzalutamide with strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) or moderate CYP3A4 inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin, St John's Wort) may decrease the plasma exposure of enzalutamide and should be avoided if possible.

Efficacy

The efficacy of enzalutamide in patients with metastatic CRPC was assessed in 5 clinical studies including two phase 3, randomized, placebo-controlled studies, MDV3100-03 (PREVAIL) and CRPC2 (AFFIRM); phase 1 Study S-3100-1-01; phase 2 Study CRPCMDA- 1; and phase 1/2 Study 9785-CL-0111.

In the two pivotal, randomized, placebo-controlled phase 3 studies (MDV3100-03 and CRPC2) in men with metastatic CRPC, enzalutamide treatment showed a statistically significant advantage over placebo across multiple clinically relevant endpoints such as overall survival, radiographic progression-free survival (rPFS), time to first skeletal-related event, time to prostate-specific antigen (PSA) progression, PSA response rate, best overall soft tissue response, and quality of life as measured by the Functional Assessment of Cancer Therapy - Prostate (FACT-P). Notably, in MDV3100-03, a study of enzalutamide versus placebo in men with metastatic CRPC who were chemotherapy-naïve, enzalutamide delayed time

to initiation of cytotoxic chemotherapy compared with placebo. In both phase 3 studies of patients with metastatic CRPC, the benefit of enzalutamide treatment on overall survival as measured by the estimated hazard ratio was observed across all prespecified subgroups. A significant benefit on overall survival was observed despite substantially higher and earlier use in the placebo groups of subsequent therapies that are known to have a survival benefit in patients with prostate cancer. Further data from open-label Studies S-3100-1-01, CRPC-MDA-1, and 9785-CL-0111 in patients with metastatic CRPC provided supportive efficacy information.

Overall Safety Profile:

The safety data cut-off date for this information is 01 June 2014, unless otherwise specified.

The efficacy and safety of enzalutamide in 4692 patients with CPRC were demonstrated in four randomized, multicenter clinical trials (AFFIRM, PREVAIL, TERRAIN, and PROSPER). Three trials were placebo-controlled and one trial was bicalutamide-controlled. Patients received enzalutamide 160 mg (2784 patients) or placebo orally one daily (1708 patients) or bicalutamide 50 mg orally once daily (189 patients).

The most common adverse reactions (≥ 10%) that occurred more frequently (≥ 2% over placebo) in the XTANDI-treated patients from the randomized placebo-controlled clinical trials were asthenia/fatigue, decreased appetite, hot flush, arthralgia, dizziness/vertigo, hypertension, headache, and weight decreased.

Seizures

In Study 1, 7 of 800 (0.9%) of patients treated with enzalutamide experienced a seizure and no patients treated with placebo experienced a seizure. Seizure occurred from 31 to 603 days after initiation of enzalutamide. In Study 2, 1 or 871 (0.1%) of chemotherapy-naïve patients treated with enzalutamide and 1 of 844 (0.1%) of patients treated with placebo experience a seizure. Patients experiencing seizure were permanently discontinued from therapy and all seizure events resolved. There is no clinical trial experience re-administering enzalutamide to patients who experienced seizure.

Laboratory Abnormalities

In the two randomized clinical trials, grade 1-4 neutropenia occurred in 15% of patients treated with enzalutamide (1% G3/4) and in 6% of patients treated with placebo (0.5% G3/4). The incidence of G1-4 thrombocytopenia was 6% of patients treated with enzalutamide (0.3% G3/4) and 5% of patients treated with placebo (0.5% G3/4). Grade 1-4 elevations in ALT occurred in 10% of patients treated with enzalutamide (0.2% G3/4) and 16% of patients treated with placebo (0.2% G3/4). Grade 1-4 elevations in bilirubin occurred in 3% of patients treated with enzalutamide (0.1% G3/4) and 2% of patients treated with placebo 0% G3/4).

Infections

In Study 1, 1% of patients treated with enzalutamide compared to 0.3% of patients treated with placebo died from infections or sepsis. In Study 2, 1 patient in each treatment group (0.1%) had an infection resulting in death.

Falls and Fall-related Injuries

In the two randomized control trials, falls including fall-related injuries, occurred in 9% of patients treated with enzalutamide compared to 4% of patients treated with placebo. Falls were not associated

with loss of consciousness or seizure. Fall-related injuries were more severe in patients treated with enzalutamide and included non-pathologic fractures, joint injuries and hematomas.

Hypertension

In the two randomized control trials, hypertension was reported in 11% of patients receiving enzalutamide and 4% of patients receiving placebo. No patients experienced hypertensive crisis. Medical history of hypertension was balanced between the two arms. Hypertension led to study discontinuation in < 1% of patients in each arm.

Post-Marketing Experience

The following additional adverse reactions have been identified during the post approval use of enzalutamide. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Neurological Disorders: posterior reversible encephalopathy syndrome (PRES)

PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI).

Two postmarketing cases of confirmed PRES were identified from the global safety database (estimated cumulative postmarketing exposure of 17704 patient treatment years as of 30 August 2014).

Discontinuation of enzalutamide in patients who develop PRES is recommended. Patients should be informed to contact the study physician as soon as possible if they experience rapidly worsening symptoms possibly indicative of PRES such as seizure, headache, confusion, reduced eyesight, or blurred vision.

Early Results from Trials in Women with Breast Cancer

Emerging data from one phase 1 and two phase 2 studies in female breast cancer patients demonstrate a safety profile consistent with the safety profile of enzalutamide in men with prostate cancer.

2.2 Endometrial Cancer:

Endometrial cancer is the most common gynecologic tumor, accounting for 10,170 deaths in 2015[2]. Fortunately, most cases are early stage at presentation where long-term survival is common. Patterns of recurrence are more common in advanced stage disease and high-risk histologic subtypes. Outside of local disease failures, limited options are available for the majority of patients with distant disease. The best treatment options yield response rates from 15-50% in the recurrent setting, with an approximate progression free survival of 6-14 months[3, 4]. One key gap in knowledge to maximize care of patients with endometrial cancer is prioritization of agents to combine with current standard of care chemotherapy. Those patients with advanced disease are unlikely to be cured by surgery or radiation alone. In addition, the prognosis for recurrent disease is even more dismal, with expected overall survival of only 14-15 months. Much work needs to be done with regards to managing patients with advanced stage or recurrent disease. The current standard is systemic treatment with paclitaxel and carboplatin. A large phase III non-inferiority study performed by the Gynecologic Oncology Group (GOG) compared paclitaxel/carboplatin versus a three drug regimen of paclitaxel, doxorubicin and cisplatin (TAP) and showed that paclitaxel/carboplatin was not inferior to TAP in terms of progression free survival (PFS) and overall survival (OS). In addition, paclitaxel and carboplatin had a favorable toxicity profile[4]. Recent

studies through the GOG, including GOG286B, have focused on the combination of novel targeted agents with paclitaxel and carboplatin. Final results from these studies are eagerly anticipated. The proposed study will evaluate the addition of androgen receptor targeting to this standard of care combination.

Endometrial cancer has been well characterized through collaborations including The Cancer Genome Atlas (TGCA), providing necessary data to employ targeted agents[5]. Regrettably, the potential for targeted therapy has not been reached, with only short-lived clinical responses despite use of agents directed at common aberrations. Given the success of endocrine therapy for breast cancer, the estrogen receptor (ER) has been considered as a target in endometrial cancer with limited success. Treatment of recurrent and progressive tumors with progestins and progestins in combination with tamoxifen (a selective estrogen receptor modulator) has been evaluated[6-9]. In GOG 81, medroxyprogesterone acetate at 200 mg daily resulted in an objective response rate of 25% (36/145 patients)[7]. Median duration of response was short (3.2 months). In GOG 119, single arm phase II trial of medroxyprogesterone acetate plus tamoxifen (tamoxifen 20 mg BID with medroxyprogesterone acetate 100 mg BID given on alternating weeks) showed a 33% (19/58 patients) objective response rate[8]. Again, median progression free survival was short (3 months). In a phase II study by the Gynecologic Oncology Group, an aromatase inhibitor (anastrozole) had limited activity as a single agent against recurrent and progressive endometrial cancer[10]. In this study, of the 23 patients enrolled, two had partial responses (9%) and two had short-term stable disease

The androgen receptor (AR) is even more widely expressed in endometrial cancer as compared to ER, with up to 90% of cases positive[11, 12]. Of note, AR expression is primarily found in the endometrioid histology type, with decline in expression as grade of tumor increases. Additional support for anti-androgen therapy comes from literature which demonstrates that androgens have clear anti-proliferative effects in the endometrium. Preclinical studies have demonstrated that androgen-dependent signaling leads to growth inhibition of endometrial cancer cell lines[13]. In addition the impact of reducing AR-regulated transcription may also yield benefits in endometrial cancer. Specifically, cyclin D1, which is a prognostic factor for endometrial cancer, is AR-regulated[14]. Finally, KRAS protein expression has also been identified as AR-regulated in breast cancer[15]. Given that KRAS is mutated in approximately 20% of endometrial cancer, reduction of this target may have impact on clinical outcome. Thus, use of novel AR-inhibitors, such as enzalutamide, holds great promise for patients with endometrial cancer.

2.3 Prediction of response to AR-inhibitors in Endometrial Cancer

Our current experience with targeted therapy in endometrial cancer has revealed that despite a high prevalence of molecular aberrations, response to rationally targeted agents in unselected cases is minimal. An additional gap in knowledge preventing provision of ideal individualized care to women with endometrial cancer is identification of which patients will benefit from treatment with a given targeted agent. Discovery of predictive markers of response and resistance to therapy is paramount. In the case of enzalutamide, key questions include importance of activation of AR and identification of relevant mechanisms of resistance to inform future combinations.

The androgen receptor is highly expressed in endometrioid endometrial cancer and appears to have a role in risk of endometrial cancer development[11, 12, 15]. Further, it appears that growth of endometrial cancer cell lines is inhibited by androgen-dependent signaling[12, 16]. Thus, this is a rational target for the treatment of endometrial cancer. Enzalutamide is a novel AR-inhibitor that has been successfully employed for the treatment of castration-resistant prostate cancer. To date, there have been few studies on the prediction of response to enzalutamide. Certainly, expression and activation of AR are

reasonable candidates for identification of potential response to therapy. In addition, the AR-V7 splice variant and elevated chromogranin-A have been explored as potential predictors of response to therapy[17-19]. The exploration of predictors of response and resistance to enzalutamide in endometrial cancer is paramount. We plan to use established molecular techniques, including sequencing and reverse phase protein lysate array (RPPA) to identify genomic aberrations and potential predictors of response. RPPA is a high throughput, functional proteomics tool that can quantify protein expression in a target, as well as, others in pathways of interest, simultaneously, and from small aliquots of tissue. Post-translational modifications, such as phosphorylation, are important indicators of activity of many signaling pathways. We have implemented RPPA to examine the effects of PI3K and RAS pathway inhibitors in patient biopsies[20, 21]. RPPA provides a rational method to identify early pharmacodynamic effects of targeted agents in clinical trials. Our group published the use of RPPA to identify pharmacodynamic markers of efficacy for perifostine, an AKT inhibitor currently in phase III trials. Utilizing pre- and post-treatment biopsies in a group of patients with advanced solid tumors, we identified a correlation between early downregulation of phosphorylated AKT and pS6 and anti-tumor activity[20] . This has the potential to reduce the duration and cost of clinical trials while improving overall patient outcomes by allowing early transition to a more effective therapy. The use of RPPA to detect early responders based on changes in post-treatment biopsies also has the potential to impact the clinical care of patients, allowing for early transition to new therapies in the case of non-response. In addition, assessment of protein levels in non-responding patients may allow identification of potential resistance mechanisms. These findings can be taken from bedside to bench, elucidating mechanisms of resistance as well as to direct future combinations.

We hypothesize that molecular aberrations, including androgen receptor (AR) activation, will predict for response to enzalutamide. Further, use of a comprehensive molecular platform will allow for identification and implementation of approaches to optimally select patients likely to benefit (or not benefit) from AR inhibition and inform future rational combinations.

3.0 PATIENT SELECTION

The target population is women ≥ 18 years of age with advanced (measurable FIGO stage III or FIGO stage IV) or recurrent endometrioid endometrial cancer who have received no prior chemotherapy. Patients must have measurable and biopsy-accessible disease.

3.1 Inclusion Criteria

3.1.1 Patients must have a histologically confirmed diagnosis (by either primary surgical specimen or biopsy for recurrence) of advanced stage (stage III or IV) or recurrent endometrioid endometrial cancer or mixed endometrioid.

3.1.2 Measurable disease (at least one measurable lesion) IS required. A measurable lesion is one that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be > 10 mm when measured by CT scan, MRI, or caliper measurement by clinical exam; or > 20 mm when measured by Chest X-Ray. Lymph nodes must be > 15 mm in short axis when measured by CT or MRI (See Section 10 for the evaluation of measurable disease).

3.1.3 Patients must have at least one “target lesion” to be used to assess response on this protocol as defined by RECIST (Section 10). Tumors within a previously irradiated field will be designated as “non-target” lesions unless progression is documented or a biopsy

is obtained to confirm persistence at least 90 days following completion of radiation therapy.

3.1.4 Patient with an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1. Please refer to Appendix A.

3.1.5 Life expectancy of greater than 3 months in the opinion of the principal investigator.

3.1.6 Recovery from effects of recent surgery, radiotherapy, or chemotherapy.

3.1.7 Patients should be free of active infection requiring antibiotics (with the exception of uncomplicated UTI).

3.1.8 Any hormonal therapy directed at the malignant tumor must be discontinued at least one week prior to registration.

3.1.9 Any other prior therapy directed at the malignant tumor, including immunologic agents, must be discontinued at least three weeks prior to registration.

3.1.10 PRIOR THERAPY: Patients should have had **NO** prior chemotherapy agents for advanced or recurrent endometrial cancer. Prior chemotherapy administration in conjunction with primary radiation therapy as a radiosensitizer would **NOT** exclude a patient from participation in this trial.

3.1.11 Patients must have adequate:

3.1.11.1 Bone marrow function: Absolute neutrophil count (ANC) greater than or equal to 1,500/mcl, equivalent to Common Terminology Criteria (CTCAE v4.03) grade 1. Platelets greater than or equal to 100,000/mcl.

3.1.11.2 Renal function: calculated creatinine clearance (Cockcroft-Gault formula) > 50 ml/min OR 24-hour urine creatinine clearance > 50 ml/min.

3.1.11.3 Hepatic function: Bilirubin less than or equal to 1.5 x ULN (CTCAE v4.03 grade 1; in patients with known Gilbert Syndrome, a total bilirubin ≤ 3.0 x ULN, with direct bilirubin ≤ 1.5 x ULN). AST and alkaline phosphatase ≤2.5 x ULN (CTCAE v4.03 grade 1); AST and ALT ≤ 3 x ULN (or ≤ 5.0 x ULN if hepatic metastases are present).

3.1.11.4 Neurologic function: Neuropathy (sensory and motor) less than or equal to CTCAE v4.03 grade 1.

3.1.11.5 PT such that international normalized ratio (INR) is ≤ 1.5 (or an in-range INR, usually between 2 and 3, if a patient is on a stable dose of therapeutic warfarin) and a PTT ≤ 1.5 times the institutional upper limit of normal. Patients receiving low molecular weight heparin for the prevention or treatment of venous thromboembolic disease are eligible if considered clinically stable on their regimen.

3.1.12 Patients must have signed an approved informed consent.

3.1.13 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of enzalutamide in combination with carboplatin and paclitaxel in patients <18 years of age, children are excluded from this study.

3.1.14 The effects of enzalutamide on the developing human fetus are unknown. For this reason and because therapeutic agents used in this trial may be teratogenic, women of child-bearing potential and their partners must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Women of child-bearing potential (intact uterus) should have a negative serum pregnancy test. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Patients must be able to swallow whole tablets.

3.1.15 With the exception of alopecia, any unresolved toxicities from prior chemotherapy should be no greater than CTCAE (Version 4.03) Grade 1 at the time of starting study treatment.

3.1.16 Patients on the Phase II portion only must be willing to undergo pre- and post-treatment biopsies and have at least one lesion amenable to biopsy.

3.2 Exclusion Criteria

3.2.1 Patients who have isolated recurrences (vaginal, pelvic, or paraaortic) that are amenable to potentially curative treatment with radiation therapy or surgery.

3.2.2 Patients with any component of the following histologies of endometrial cancer are not eligible for enrollment: serous adenocarcinoma, adenosquamous carcinoma, mucinous adenocarcinoma, carcinosarcoma, and sarcoma.

3.2.3 Prior Therapy:

Prior Chemotherapy: Patients who have had a prior chemotherapy regimen for advanced or metastatic disease are excluded.

Prior Radiation Therapy: Patients may have received prior radiation therapy for treatment of endometrial carcinoma. Prior radiation therapy may have included pelvic radiation therapy, extended field pelvic/para-aortic radiation therapy, and/or intravaginal brachytherapy, alone or with chemotherapy as a radiation sensitizer. All radiation therapy must be completed at least 4 weeks prior to the first date of study therapy. The prior radiation field, radiation dose, number of fractions and prior radiation start and stop dates must be provided at registration.

3.2.4 Patients who have previously received enzalutamide. Patients may have received prior hormonal therapy for treatment of endometrial carcinoma. All hormonal therapy must be discontinued at least one week prior to the first date of study therapy.

3.2.5 Patients who have had radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events (CTCAE v4.03 grade 2 or greater, excluding alopecia) due to agents administered more than 4 weeks earlier.

3.2.6 Patients may not receive any other anti-neoplastic or investigational agents within 3 weeks of study enrollment. Patients may not be receiving any other investigational agents during treatment on protocol.

3.2.7 Patients may not receive strong CYP2C8 inhibitors, CYP2C8 inducers, or CYP3A4 inducers. In addition, patients should not receive drugs that are metabolized by CYP3A4 or CYP2C9 (Appendix D).

3.2.8 Patients who are pregnant or nursing. The effects of enzalutamide on the developing human fetus are unknown. For this reason women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.2.9 Patient had major surgery within 28 days prior to starting study drug or has not recovered from major side effects of the surgery.

3.2.10 Patients may not have a history of other malignancies except for basal cell or squamous cell skin cancer, in situ cervical cancer, unless they have been disease-free for at least five years.

3.2.11 Patients with predisposing factors for seizure including history of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain metastasis, and brain arteriovenous malformation.

3.2.12 Patient with history of allergic reactions or hypersensitivity attributed to compounds of similar chemical or biologic composition to enzalutamide, carboplatin, or paclitaxel.

3.2.13 Patients may not have symptomatic, uncontrolled spinal cord compression and/or brain metastases. A scan to confirm absence of brain metastasis is not required. Patients can receive a stable dose of corticosteroids before/ during study if these were started at least 28 days prior to entry.

3.2.14 As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases (e.g., severe hepatic impairment, interstitial lung disease [bilateral, diffuse, parenchymal lung disease], uncontrolled chronic renal diseases [glomerulonephritis, nephritic syndrome, Fanconi Syndrome or Renal tubular acidosis]), or current unstable or uncompensated respiratory or cardiac conditions, or uncontrolled hypertension (blood pressure ≥ 160/90), active bleeding diatheses or active infection including hepatitis B, hepatitis C, and human immunodeficiency virus. Screening for chronic conditions is not required.

3.2.15 As judged by the Investigator, the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions, and requirements.

3.3 Inclusion of Women and Minorities:

Women and members of all races and ethnic groups are eligible for this trial. MDACC will not exclude any potential subject from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the MDACC cancer population.

4.0 TREATMENT PLAN

This is a single arm, open-label phase II study with a limited safety lead in of the novel AR-inhibitor, enzalutamide, in combination with paclitaxel and carboplatin in previously untreated patients with advanced and recurrent endometrioid endometrial cancer. All patients will be registered in the MD Anderson Clinical Oncology Research System (CORe).

After Cycle 3, patients may undergo clinically indicated, standard-of-care tumor reduction surgery and remain on study.

4.1 Safety Lead-In (Part A)

In the safety lead-in (Part A), 6 patients will be treated with the combination of enzalutamide and standard IV carboplatin and paclitaxel as per Table 1.

Combination Therapy: Enzalutamide, Paclitaxel and Carboplatin (Cycles 1-9)

- Paclitaxel IV over 3 hours day 1
- Carboplatin IV over 1 hour day 1
- Enzalutamide PO daily day 1-21
- Every 21 days x 6-9 cycles

Dose-limiting toxicities (DLTs) will be evaluated during this safety lead-in. The period for evaluating DLTs will be from the time of first administration of treatment until the completion of the first cycle of therapy (21 days). Subjects who do not remain on the study up to this time for reasons other than DLT will be replaced with another subject at the same dose level. Grading of DLTs will follow the guidelines provided in CTCAE version 4.03.

A DLT is defined in this study as any of the following:

1. Any grade 3 or 4, non-hematologic, treatment-related toxicity using the CTC-AE criteria 4.03 (excluding nausea, vomiting, dehydration, diarrhea, fatigue or asymptomatic electrolyte abnormality [hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, and hypophosphatemia]).
2. Any grade 4, treatment-related, non-neutropenic, hematologic toxicity or any grade treatment-related neutropenia lasting more than 7 days.
3. Any treatment-related hematologic toxicity requiring treatment delay beyond 2 weeks.
4. Any grade 3 or 4 nausea, vomiting, diarrhea, dehydration or fatigue which persists for more than 72 hours despite maximally supportive care.
5. Any grade 3 or 4 electrolyte abnormality (including hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, and hypophosphatemia) which is not corrected to ≤ grade 1 within 72 hours should be considered a dose-limiting toxicity even if patient is asymptomatic.

6. Any grade 3 thrombocytopenia with clinically significant bleeding.
7. Grade 4 thrombocytopenia of any duration.
8. Febrile neutropenia.

Unless specified above, any other Grade 3 or higher toxicity that occurs during the DLT evaluation period will be considered a DLT. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition.

Table 1. Dose Levels for Safety Lead-in

Dose Level	Enzalutamide		Dose Level	Paclitaxel		Dose Level	Carboplatin
1	160 mg PO		1	175 mg/m^2		1	AUC 5
-1	120 mg PO		-1	175 mg/m^2		-1	AUC 5
-2	80 mg PO		-2	150 mg/m^2		-2	AUC 4
-3	Off		-3	135 mg/m^2		-3	OFF

For Grade 3 or higher toxicities, other than neuropathy, hold the dose for one week, and then reinstitute therapy if symptoms have resolved to Grade 2 or below. If the symptoms remain Grade 3 or above for that week, then the toxicity will be considered a DLT, and the dose will be reduced. For neuropathy Grade 3 or above, please refer to Table 4 for guidance.

Patients will be treated in cohorts of 3. The first 3 patients will be treated at dose level 1, if 1 or fewer patient experiences a DLT in cycle 1, 3 more patients will be treated at dose level 1; otherwise deescalate the dose to level -1. If 2 or fewer patients out of 6 experience DLTs, then the regimen will be deemed safe for administration in the phase II study; otherwise deescalate the dose to level -1. At dose level -1, the same rule will be used to determine dose selection and deescalation.

The maximum number of cycles is 6-9 in the absence of toxicity, progression, or patient death. If this dose combination is not tolerated, the agents will be dose reduced until a tolerable combination dose is identified or deemed infeasible. Once the combination dose is identified, phase II enrollment will continue per the statistical plan in section 12.0 Statistical Considerations. Dose modifications guidelines are detailed in section 5.0 Dosing Delays/Modifications. Pharmacokinetic (PK) samples will be collected as described in sections 4.3 and Appendix B. Please see section 9.0 Study Calendar for study assessments.

4.2 Phase II (Part B)

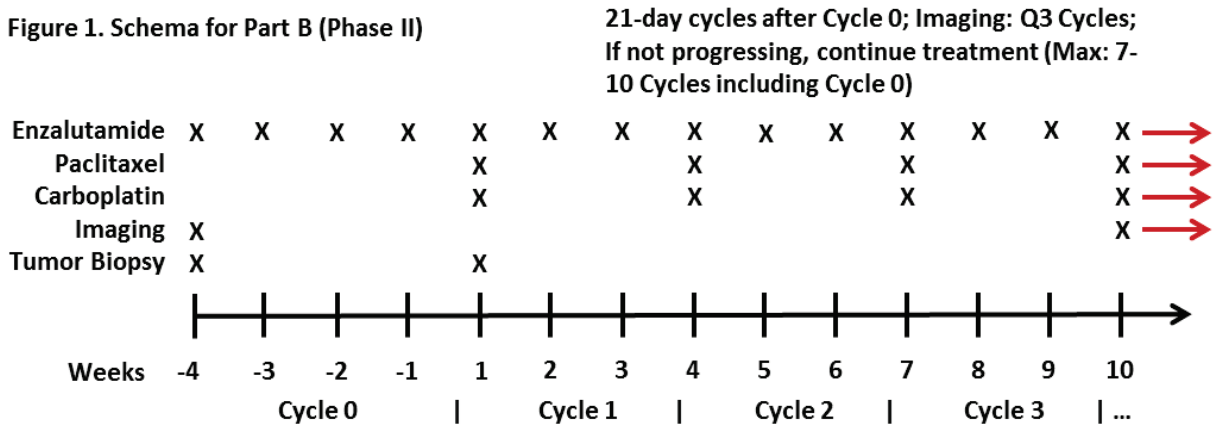
Patients on the phase II portion of study (Part B) will undergo induction treatment with enzalutamide single agent at 160 mg PO daily orally for 28 days (Cycle 0). Biopsies will be obtained pre-treatment and 26-28 days after treatment initiation. After the post-treatment biopsy and within 3-5 days of completing Cycle 0, patients will be initiated on combination therapy of enzalutamide, paclitaxel, and carboplatin. Please see Figure 1. Patients will be treated with Enzalutamide daily and Paclitaxel and Carboplatin on day 1 every 21 days for 6-9 cycles or until progression of disease or adverse events prohibit further therapy. Baseline imaging will be obtained prior to enzalutamide single agent treatment and prior to initiation of the combination therapy.

Combination treatment with Enzalutamide, Paclitaxel and Carboplatin (Cycles 1-9) will initiate 3 to 5 days following completion of cycle 0.

Response will be measured every 3 cycles during the 6-9 cycles and then 3 weeks after the last treatment (or if clinical suspicion warrants assessment). Response will be assessed using RECIST version 1.1. Patients will be considered responders if they achieve an objective confirmed CR or PR 3 weeks after completion of Cycle 6. Responders may be continued on three additional cycles of chemotherapy at the discretion of the primary treating physician.

Dose modifications guidelines are detailed in section 5.0 Dosing Delays/Modifications. Pharmacokinetic (PK) samples will be collected as described in sections 4.3 and Appendix B. Please see section 9.0 Study Calendar for study assessments.

Figure 1. Schema for Part B (Phase II)



4.3 Pharmacokinetics (PK) for Part A and Part B:

Pharmacokinetics (PK) will be assessed on all patients during the first stage of accrual (n=20). This will include the patients on the safety lead in (from 6 to 12 possible subjects) and the first patients (from 8 to 14) in the phase II portion of the study. PK assessments will be performed during Cycle 2 after enzalutamide has reached the steady state. Enzalutamide and paclitaxel are both major substrates and inducers of CYP3A4. Enzalutamide is a strong inducer of CYP3A4 and paclitaxel is considered a weak inducer of CYP3A4. Carboplatin is not affected by CYP enzymes, therefore, there is no anticipated PK interaction. As enzalutamide half-life is 5.8 days and time to peak is 1 hour (range 0.5 to 3 hours), PK draws for enzalutamide will be performed at baseline, 0.5, 1, 2 and 4 hours. We will also evaluate PK regarding enzalutamide potential effect on paclitaxel metabolism. Paclitaxel's alpha t1/2 is 16 minutes, beta t1/2 is 140 minutes and terminal t1/2 is 13-20 hours. Thus, PK draws for paclitaxel will be performed at baseline, 15 minutes after infusion completion, 0.5 hours after infusion completion, 2 hours after infusion completion and 4 hours after infusion completion. This will be a total of 9 PK draws during the second combination cycle. See Appendix B for full details.

4.4 Enzalutamide Administration

Enzalutamide will be provided by Astellas/Medivation. Treatment will be administered on an outpatient basis. Patients will take 4 capsules (40 mg capsules) in the morning for a total daily dose of 160 mg with or without a meal. Capsules should be swallowed whole, they should not be crushed or cut. The dosing time may be adjusted as required. If doses are missed for toxicity, they should not be replaced. If a dose is not taken due to an error, it may be taken up to 12 hours later. If vomiting occurs within 30 minutes of intake, that dose may be repeated.

Patients who will be providing PK blood samples will be instructed to bring their dose to CTRC to be taken in the presence of a nurse to ensure PK time points.

Patients will be provided with a Medication Diary for enzalutamide (Appendix C), instructed in its use, and asked to bring the diary with them to each appointment. In addition, the patients should bring any unused tablets with them to each appointment. A new copy of the Medication Diary will be given to patients whose dose is reduced due to adverse events.

Reported adverse events and potential risks are described in Section 6. Appropriate dose modifications for enzalutamide are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

4.5 General Concomitant Medication Guidelines

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study with reasons for the treatment should be recorded. If medically feasible, patients taking regular medication should be maintained on it throughout the study period. The investigator should instruct the patient to notify the study nurse about any new medications she takes after initiating the study. All supportive measures consistent with optimal patient care will be given throughout the study. Bisphosphonates, topical medications, antiemetics, anti-diarrheal medications, anticoagulants, and antibiotics may be used at the discretion of the treating physician.

The administration of any other anticancer agents, including chemotherapy and biologic agents is not permitted. Similarly, the use of other investigational drugs is not allowed. Patients requiring anti-cancer therapies other than the study medication, with the exception of palliative radiotherapy, must be discontinued from the study. Prophylactic use of myeloid growth factors (e.g., G-CSF or GM-CSF) is not allowed. However, use of myeloid growth factors for neutropenia is acceptable.

Patients may not receive strong CYP2C8 inhibitors, CYP2C8 inducers, or CYP3A4 inducers. In addition, patients should not receive drugs that are metabolized by CYP3A4 or CYP2C9 (Appendix D).

All medications (prescriptions or over-the-counter medications) continued at the start of the trial or started during the study or until 30 days from the end of the last protocol treatment and different from the study medication must be documented.

4.6 Dosing of Paclitaxel

Paclitaxel will be administered on a 21-day (+7 day) schedule. Paclitaxel (175 mg/m^2) IV will be infused over 3 hours on day #1 of each cycle.

Maximum body surface area used for dose calculations will be 2.2 m^2.

Paclitaxel will be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Nothing else should be infused through this IV line.

All patients should receive premedication before the administration of paclitaxel in order to prevent severe hypersensitivity reactions. A typical premedication regimen consists of the following given 30-60 minutes prior to paclitaxel: 10-20 mg intravenous (IV) dexamethasone, 50 mg IV diphenhydramine (or its equivalent), and 20 mg IV famotidine (pepcid). The dexamethasone dose may be increased or the patient may be treated with a paclitaxel desensitization protocol at the investigator’s discretion if a patient experiences a hypersensitivity reaction when given paclitaxel. Alternatively if a patient experiences a hypersensitivity reaction to paclitaxel after cycle 2 the paclitaxel may be discontinued and she may continue being treated on protocol with the other study drugs at the investigator’s discretion.

Patients who experience toxicities that may be related to paclitaxel may switch to docetaxel, under the approval of the principal investigator.

4.7 Dosing of Carboplatin

Carboplatin will be administered on a 21-day (+7 day) schedule. Carboplatin (AUC 5) calculated dose in 250ml D5W IV will be infused over 1 hour on day #1 of each cycle.

Carboplatin dose will be based on the Calvert formula:

Carboplatin dose (mg) = AUC x (GFR + 25)

GFR is estimated using the Cockcroft-Gault formula for creatinine clearance:

(140 - patient's age) x (patient's weight in kilograms)

72 x patient's serum creatinine

(multiply the result by 0.85; for serum creatinine less

than 0.7, a minimum creatinine value of 0.7 should be assigned)

Actual, not ideal body weight will be used.

This value will substitute for GFR in Calvert formula.

NOTE: the GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min, such that

Maximum carboplatin dose (mg) = target AUC(mg•min/mL) • 150 mL/min.

The maximum carboplatin dose should not exceed target AUC (mg•min/mL)•150 mL/min. For a target carboplatin AUC of 5, the maximum dose would be 750 mg.

4.8 Carboplatin Hypersensitivity:

The patient may be treated with a carboplatin desensitization protocol at the investigator's discretion if a patient experiences a hypersensitivity reaction when given carboplatin. Alternatively if a patient experiences a hypersensitivity reaction to carboplatin the carboplatin may be discontinued and she may continue being treated on protocol with the other study drugs at the investigator's discretion.

4.9 Criteria for removal from treatment

- Inability to tolerate enzalutamide, paclitaxel, and/or carboplatin at the lowest doses because of toxicity,
- Patients may withdraw from the study at any time for any reason,
- Patients with evidence of disease progression,
- Unacceptable adverse event(s),
- Intercurrent illness that prevents further administration of treatment,
- Onset of seizure or PRES
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

4.10 Duration of Follow Up

Patients will be followed for 52 weeks after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.0 DOSING DELAYS/DOSE MODIFICATIONS

Each study drug may be dose reduced individually. Enzalutamide dose modification may occur in light of Enzalutamide-related toxicity when administered alone during cycle 0 for patients enrolled in Phase II (Part B) as well as when administered in combination with Paclitaxel and Carboplatin during cycle 1 and subsequent cycles for patients enrolled in the Safety Lead-in (Part A) and Phase II (Part B). Paclitaxel and Carboplatin dose modifications may not occur in cycle 1 and are only applicable to subsequent treatment cycles. Each dose reduction of Enzalutamide, Paclitaxel and/or Carboplatin will be based upon the toxicity. No further dose reductions below those specified in Table 2 will be allowed. All dose reductions are permanent, that is, there will not be any re-escalation of study drugs.

For Grade 3 or higher toxicities, other than neuropathy, hold the dose for one week, and then reinstitute therapy if symptoms have resolved to Grade 2 or below. If the symptoms remain at Grade 3 or above for that week, then the dose will be reduced. For neuropathy Grade 3 or above, please refer to Table 4 for guidance.

Table 2. Dose-reduction Schedules for Phase II

Dose Level	Enzalutamide		Dose Level	Paclitaxel		Dose Level	Carboplatin
1	160 mg PO		1	175 mg/m^2		1	AUC 5
-1	120 mg PO		-1	175 mg/m^2		-1	AUC 5
-2	80 mg PO		-2	150 mg/m^2		-2	AUC 4
-3	Off		-3	135 mg/m^2		-3	OFF

5.1 Hematologic toxicity

5.1.1 Initial treatment modifications will consist of cycle delay and/or dose reduction as indicated in the Table 3. The use of hematopoietic cytokines and protective reagents are restricted as noted:

5.1.1.1. Patients will NOT receive prophylactic growth factors [filgrastim (G-CSF), sargramostim (GM-CSF), pegfilgrastim (Neulasta)] unless they experience recurrent neutropenic complications after treatment modifications specified below.

5.1.1.2. No platelet growth factors are allowed.

5.1.1.3. Patients may receive red blood cell growth factors for management of anemia based on institutional guidelines.

5.1.2 Treatment decisions will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC).

5.1.3 Subsequent cycles of chemotherapy (paclitaxel and carboplatin) will not begin until the ANC is $\geq$ 1000 cells/mm^3 (CTC grade 2) and the platelet count is $\geq$ 75,000/uL. Therapy will be delayed for a maximum of four weeks until these values are achieved. However, therapy with enzalutamide may resume when platelets ≥50,000/mm^3 during this delay period. Patients who fail to recover adequate counts within a four-week delay will be removed from study.

Table 3. Dose Modifications for Hematologic Toxicity

Toxicity NCI CTCAE Grade[1]	**Paclitaxel Dose At the Start of Subsequent Cycles of Therapy[2,3]**	**Carboplatin Dose At the Start of Subsequent Cycles of Therapy[2,3]**	**Enzalutamide Dose At the Start of Subsequent Cycles of Therapy**
Neutropenia			
1 (LLN– 1500-/mm^3)	Maintain dose level.	Maintain dose level.	Maintain dose level.
2 (1500-1000/mm^3)	Maintain dose level.[4]	Maintain dose level.[4]	Maintain dose level.
3 (1000-500/mm^3)	Hold treatment for a maximum of 4 weeks until recovered to ≤ Grade 1. Maintain dose level.[4]	Hold treatment for a maximum of 4 weeks until recovered to ≤ Grade 1. Maintain dose level.[4]	Hold treatment for a maximum of 4 weeks until recovered to ANC ≥ 1000. Maintain dose level.[4]
4 (< 500/mm^3)	Hold treatment for a maximum of 4 weeks until recovered to ≤ Grade 1. Maintain dose level.[5, 6]	Hold treatment for a maximum of 4 weeks until recovered to ≤ Grade 1. Maintain dose level.[5, 6]	Hold treatment for a maximum of 4 weeks until recovered to ANC ≥ 1000. Maintain dose level.[6]
Neutropenic fever or grade 4 neutropenia lasting >7 days [5]	Hold therapy for a maximum of 4 weeks until recovered to ≤ Grade 1 and reduce paclitaxel dose one level. [5, 6]	Hold therapy for a maximum of 4 weeks until recovered to ≤ Grade 1 and reduce carboplatin dose one level.[5, 6]	Hold therapy for a maximum of 4 weeks until recovered to ANC ≥ 1000. Maintain dose level.[6]
Thrombocytopenia			
1 (< LLN-75,000/mm^3)	No hold required. Maintain dose level.	No hold required. Maintain dose level.	Maintain dose level.
2 (75,000-50,000/mm^3)	Hold treatment for a maximum of 4 weeks until platelets have resolved to >75,000/mm^3. Maintain dose level.[4]	Hold treatment for a maximum of 4 weeks until platelets have resolved to >75,000/mm^3. Maintain dose level.[4]	Maintain dose level.

3 (50,000-25,000/mm^3)	Hold treatment for a maximum of 4 weeks until platelets have resolved to >75,000/mm^3. Maintain dose level. For grade 3 thrombocytopenia complicated by bleeding, petechiae or requiring platelet transfusion reduce paclitaxel dose one level.[4]	Hold treatment for a maximum of 4 weeks until platelets have resolved to >75,000/mm^3. Maintain dose level. For grade 3 thrombocytopenia complicated by bleeding, petechiae or requiring platelet transfusion reduce carboplatin dose one level.[4]	Hold treatment for a maximum of 4 weeks until platelets have resolved to >50,000/mm^3. Maintain dose level.
4 (< 25,000/mm^3)	Hold treatment for a maximum of 4 weeks until >75,000/mm^3. Reduce paclitaxel dose one level[,6]	Hold treatment for a maximum of 4 weeks until >75,000/mm^3. Reduce carboplatin dose one level[,6]	Hold treatment for a maximum of 4 weeks until >50,000/mm^3. Maintain dose level. [6]

1 For ≤ CTCAE v4.03 Grade 2 toxicity, maintain dose level of both agents.

2 Dose levels are relative to the starting dose in the previous cycle. Dose reductions of either paclitaxel or carboplatin below the –2 dose level will not be allowed.

3 Provided that all the retreatment criteria are met

4 Repeat lab work weekly and resume treatment based on this table.

5 For recurrent febrile neutropenia, and/or recurrent documented grade 4 neutropenia persisting ≥ 7 days after initial dose reduction see section 6.1.4. Febrile neutropenia is defined as <1.0 × 10^9/L neutrophils with fever (oral temp ≥38.5°C) or infection (documented infection with <1.0 x 10^9/L neutrophils).

6 If grade 4 neutropenia (ANC <500/mm^3) or thrombocytopenia (Platelet <25,000/mm^3), obtain twice per week until resolved to grade 3.

5.1.4 For recurrent febrile neutropenia, and/or recurrent documented grade 4 neutropenia persisting ≥ 7 days (after initial dose reduction), add prophylactic growth factors. In this circumstance, it is recommended that G-CSF at a dose of 5 μg/kg/day (or equivalent dosing of pegfilgrastim or sargramostim) will be administered subcutaneously starting the day after therapy and continuing through hematopoietic recovery. There should be a minimum of 24 hours prior to last dose of G-CSF (14 days for pegfilgrastim) before starting chemotherapy.

5.1.5 The treatment for grade 4 thrombocytopenia or grade 3 thrombocytopenia with evidence of bleeding, petechiae or requiring platelet transfusion is paclitaxel and carboplatin dose reduction. Patients who experience recurrent grade 4 thrombocytopenia or grade 3 thrombocytopenia with evidence of bleeding, petechiae or requiring platelet transfusion after one dose reduction should have a second dose reduction as noted in Table 3. Patients who experience recurrent grade 4

thrombocytopenia or grade 3 thrombocytopenia with evidence of bleeding, petechiae or requiring platelet transfusion after two dose reductions should be taken off study.

NOTE: No further dose reductions below those specified in Table 2 will be allowed. All dose reductions are permanent and there will be no dose escalation of paclitaxel or carboplatin after dose reduction.

5.2 Non-hematologic toxicity

Dose modifications should be made based on the worst preceding non-hematological toxicity and are shown in Table 4. While every effort should be made to retreat patients on time, in the case of unresolved drug-related toxicity as described below, up to a 2-week delay in treatment is permissible. If, after the dose delay, the toxicity has not fully resolved and, in the investigator's opinion, the patient can safely continue with treatment, the dose in the next cycle will be reduced as indicated in Table 4. If toxicity recurs following the second dose reduction, the patient will be withdrawn from the study treatment.

Dose modification is required for any drug-related Grade 3 or 4 non-hematologic toxicity excluding hypersensitivity reactions (see Table 4).

Table 4. Dose Modifications for Non-Hematologic Toxicity[1]

Toxicity NCI CTCAE Grade1	**Paclitaxel Dose At the Start of Subsequent Cycles of Therapy[2,3]**	**Carboplatin Dose At the Start of Subsequent Cycles of Therapy[2,3]**	**Enzalutamide Dose At the Start of Subsequent Cycles of Therapy**
Hypersensitivity Reactions	See Section 5.3.	See Section 5.3.	See Section 5.3.
Neuropathy			
Grade 2	Reduce paclitaxel dose one level.[4]	Maintain dose level.	Maintain dose level.

≥Grade 3	Reduce paclitaxel dose one level. If toxicity does not resolve to equal or less than grade 2 by the next cycle, reduce paclitaxel dose a second level (135mg/m^2). If toxicity does not resolve at this dose level by the next cycle, the patient will be withdrawn from treatment.[4]	Maintain dose level.	Maintain dose level.
Seizures			
Any grade	Hold treatment for a maximum of 2 weeks until recovered to ≤ Grade 1. Reduce paclitaxel dose one level.[4]	Maintain dose level.	Discontinue treatment.
Renal Toxicity ≥ Grade 2	Hold treatment for a maximum of 2 weeks until recovered to ≤ Grade 1. Reduce paclitaxel dose one level.[4]	Hold treatment for a maximum of 2 weeks until recovered to ≤ Grade 1. Reduce carboplatin dose one level.[4]	Hold treatment for a maximum of 2 weeks until recovered to ≤ Grade 1. Maintain dose level.[4]
Hepatic Toxicity ≥ Grade 3	Hold treatment for a maximum of 2 weeks until recovered to ≤ Grade 1. Reduce paclitaxel dose one level.[4]	Hold treatment for a maximum of 2 weeks until recovered to ≤ Grade 1. Reduce carboplatin dose one level.[4]	Hold treatment for a maximum of 2 weeks until recovered to ≤ Grade 1. Maintain dose level.[4]
Other non-hematologic toxicities[5] ≥ Grade 3	Hold treatment for a maximum of 2 weeks until recovered to ≤ Grade 1. Reduce paclitaxel dose one level.[4]	Hold treatment for a maximum of 2 weeks until recovered to ≤ Grade 1. Reduce carboplatin dose one level.[4]	Hold treatment for a maximum of 2 weeks until recovered to ≤ Grade 1. Maintain dose level.[4]

1 For ≤ CTCAE v4.03 Grade 2 toxicity not described below, maintain dose level of all agents.

2 Provided that all the retreatment criteria are met

3 Dose levels are relative to the starting dose in the previous cycle. Dose reductions of paclitaxel and carboplatin below the –2 dose level will not be allowed.

4 Repeat lab work as clinically indicated and resume treatment based on this table.

5 With the exception of alopecia, pulmonary toxicity, or cardiac toxicity.

5.3. Treatment of Hypersensitivity Reactions

Routine premedication to prevent hypersensitivity is required (See Section 4.6). It is recommended that a preparative regimen be employed to reduce the risk associated with hypersensitivity reactions. This regimen should include dexamethasone (either IV or PO), anti-histamine H1 (such as diphenhydramine) and anti-histamine H2 such as famotidine. Injectable steroids and epinephrine should be immediately available to provide prompt treatment of any severe hypersensitivity reaction that may occur during or following study treatment. The occurrence of hypersensitivity reaction to either paclitaxel or carboplatin is not considered to be a DLT. Premedicated patients with a hypersensitivity reaction to paclitaxel or carboplatin may be retreated with a slow initial infusion, which is gradually increased to the standard infusion rate in the absence of reactions at lower rates. M.D. Anderson standard paclitaxel and carboplatin desensitization protocols may be used at the discretion of the investigator. However, patients may be removed from study following the first hypersensitivity reaction without attempting desensitization at the discretion of the investigator. Patients who experience a subsequent paclitaxel or carboplatin reaction despite desensitization may be removed from the study or may continue on study but stop further paclitaxel and/or carboplatin treatment at the discretion of the investigator.

6.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 6.1) and the characteristics of an observed AE (Section 6.2*)* will determine whether the event requires expedited (via CTEP-AERS) reporting **in addition** to routine reporting.

6.1 Expected Adverse Events for Investigational Agent (Enzalutamide)

System Organ Class Preferred Term
Blood and lymphatic system disorders
Leukopenia
Neutropenia
Ear and labyrinth disorders
Vertigo
Gastrointestinal disorders
Diarrhoea
General disorders and administration site conditions
Asthenia
Fatigue
Oedema peripheral
Injury, poisoning, and procedural complications
Fracture (non-pathologic)
Fall
Musculoskeletal and connective tissue disorders
Arthalgia
Muscular weakness
Musculoskeletal pain
Musculoskeletal stiffness
Nervous system disorders
Mental impairment disorders (including memory impairment, amnesia, cognitive disorder, disturbance in attention and mental status changes)
Cauda equina syndrome
Seizure
Dizziness
Dizziness postural
Headache
Paraesthesia
Spinal cord compression
Status epilepticus
Restless Legs Syndrome
Psychiatric disorders
Anxiety
Hallucinations
Insomnia
Renal and urinary disorders
Haematuria
Pollakiuria
Reproductive system and breast disorders
Gynecomastia[†]
Respiratory, thoracic, and mediastinal disorders
Epistaxis
Skin and subcutaneous tissue disorders
Dry skin
Pruritus
Rash
Vascular disorders
Haemotoma
Hot flush (including flushing)
Hypertension (including blood pressure increased)

†For male patients only.

6.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 6.1 above) for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are ***bold and italicized*** in the CAEPR (Section 6.1).
- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

AEs and SAEs will be recorded according to the NCI suggested criteria as listed below.

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

6.3 Serious Adverse Event Reporting (SAE) Reporting

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

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience 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.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience 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 (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

6.4 Investigator Communications with Astellas and NCCN

A copy of the SAE report must be sent (via fax or email) to Astellas and NCCN at the time the event is reported to the FDA. SAE report forms should be forwarded with supporting relevant source documents (e.g. history and physical [H&P], hospital discharge summary, autopsy report when available, results of relevant diagnostic tests completed to evaluate the event):

- Astellas Pharma Global Development – United States
  Email: Safety-us@us.astellas.com
  Fax number: (847) 317-1241
- NCCN Oncology Research Program (ORP)
  Email: ORPReports@nccn.org
  Fax number: (215) 358-7699

The following minimum information is required:

- Study number/IIT regulatory identifier
- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly (within 7 days) as necessary.

7.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

7.1 Enzalutamide

7.1.1 Other name: MDV3100

7.1.2 How Supplied: Enzalutamide is presented in a soft gelatin capsule filled with a formulation containing 40 mg of the active pharmaceutical ingredient. The approved therapeutic dose is 160 mg once daily (4 capsules, each 40 mg)

7.1.3 Storage: Store at room temperature (≤ 25 °C). For more information, please follow the storage instructions provided on the drug product label.

7.1.4 Route of Administration: Orally with or without food. Capsules should be swallowed whole and cannot be crushed or broken.

7.1.5 Availability: Orally bioavailable.

7.1.6 Agent Accountability: Drug accountability will be maintained per institutional standard and will adhere to Code of Federal Regulation Requirements for accountability.

7.2 Paclitaxel (Taxol®, NSC #673089)

7.2.1 Formulation: Paclitaxel is a poorly soluble plant product from the western yew, Taxus brevifolia. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. Paclitaxel is supplied as a sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. It is also available in 100 and 300 mg vials.

7.2.2 Solution Preparation: Paclitaxel, at the appropriate dose, will be diluted in 500-1000 ml of 0.9% Sodium Chloride injection, USP or 5% Dextrose injection, USP (D5W) (500 ml is adequate if paclitaxel is a single agent). Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexlphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized.

NOTE: Formation of a small number of fibers in solution (within acceptable limits established by the USP Particulate Matter Test for LVPs) has been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: IVEX-II, IVEX-HP or equivalent) into the IV fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

7.2.3 Storage: The intact vials can be stored in a temperature range between 2-25° C (36-77°F).

7.2.4 Stability: See FDA- approved package insert and institutional standards for stability information.

7.2.5 Supplier: Commercially available from Bristol-Myers Squibb Company.

7.2.6 Administration: See section 4.4.

7.2.7 Adverse Effects:

Hematologic: Myelosuppression

Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis

Heart: Arrhythmia, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia

Pulmonary: Pneumonitis

Blood Pressure: Hypotension, hypertension (possibly related to concomitant medication--Dexamethasone)

Neurologic: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy

Skin: Infiltration: erythema, induration, tenderness, rarely ulceration, injection-recall reactions, erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)

Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus

Liver: Increased AST, ALT, bilirubin, alkaline phosphatase and triglycerides, hepatic failure, hepatic necrosis

Other: Alopecia, fatigue, arthralgia, myalgia, light-headedness, myopathy, headaches

Other, Vision: Sensation of flashing lights, blurred vision, scintillating scotomata

*See FDA- approved package insert for a comprehensive list of adverse events associated with paclitaxel.

7.3 Carboplatin (Paraplatin®, NSC # 241240)

7.3.1 Formulation: Carboplatin is supplied as a sterile lyophilized powder available in single-dose vials containing 50 mg, 150 mg and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

7.3.2 Solution Preparation: Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 ml
150 mg	15 ml
450 mg	45 ml

These dilutions all produce a carboplatin concentration of 10 mg/ml.

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

7.3.3 Storage: Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

7.3.4 Stability: See FDA- approved package insert and institutional standards for stability information.

7.3.5 Supplier: Commercially available from Bristol-Myers Squibb Company.

7.3.6 Administration: See Section 4.5.

7.3.7 Adverse effects:

Hematologic: Myelosuppression

Gastrointestinal: Nausea, vomiting, diarrhea, abdominal pain, constipation

Neurologic: Peripheral neuropathy, ototoxicity, visual disturbances, change in taste, central nervous system symptoms

Renal: Abnormal renal function test results including serum creatinine, blood urea nitrogen, and creatinine clearance

Hepatic: Abnormal liver function tests including bilirubin, AST, and alkaline phosphatase

Electrolyte Changes: Abnormally decreased serum electrolyte values reported for sodium, potassium, calcium, and magnesium.

Allergic Reactions: Rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension.

Injection Site Reactions: Redness, swelling, pain; necrosis associated with extravasation has been reported.

Other: Pain, asthenia, alopecia. Cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in 6% or less of the patients. Cardiovascular events (cardiac failure, embolism, cerebrovascular accidents) were fatal in less than 1% of patients and did not appear to be related to chemotherapy. Cancer-associated hemolytic-uremic syndrome has been reported rarely. Malaise, anorexia, and hypertension have been reported as part of post-marketing surveillance.

*See FDA-approved package insert for a comprehensive list of adverse events associated with carboplatin.

8.0 CORRELATIVE/SPECIAL STUDIES

8.1 Collection of Specimens

1. Biopsies

- Pre-treatment (within 14 days prior to day 1 of Cycle 0)
- Post-treatment (between days 26-28 of Cycle 0)

2. Plasma samples for biomarkers

- Pre-treatment (within 14 days prior to day 1 of Cycle 0)
- Post-treatment (between days 26-28 of Cycle 0)

3. White blood cells (WBCs)

White blood cells for germline control of DNA-sequencing will be collected pre-treatment (within 14 days prior to day 1 of Cycle 0). If WBC collection is not collected pre-treatment, it may be collected between days 26-28 of Cycle 0.

4. Plasma samples for Pharmacokinetics

Plasma samples for PK analyses will be collected during Cycle 2 Week 1 for the first 20 patients (from Safety Lead-in and then Phase II). Please see Appendix B for a detailed schedule.

8.2 Handling of Specimens

Biopsies: Repeat biopsies of the same recurrent endometrial cancer must be collected at two time points from each patient when the disease is safely accessible. The biopsies will be obtained directly or by image guided techniques. A simple biopsy will be obtained for each time point when possible. Alternatively, one or more pass needle biopsies will be obtained using a 22 gauge or larger needle at the discretion of the interventional radiologist for each time point in order to obtain adequate tissue. Ideally a 16 gauge needle will be utilized. Samples will be snap-frozen within 30 minutes for further analysis.

Plasma: Whole venous blood is collected in Vacutainer tubes. Samples will be spun and the plasma aliquoted and placed in a cryotube. The samples will then be stored in the freezer at -80 degrees Celsius. Specific processing, labeling, and storing instructions are included in a separate Standard Operating Procedure.

8.3 Analysis of Tissue

Pre-treatment and post-treatment tissue will be obtained for the following analyses:

1. Targeted or whole exome sequencing for AR, MAPK and PI3K pathways;
2. Immunohistochemistry (IHC) for AR localization, transport and activation;
3. Transcriptomic analyses including Visium spatial transcriptomic assay;
4. Functional and comprehensive assays with global proteomics and reverse phase protein array (RPPA) of AR-related pathways;
5. t-cell infiltrates will be characterized using our institution's existing immunotherapy platform and informatics to determine the immunophenotype.

8.4 Methods of Analysis

Immunohistochemical studies for AR localization, transport, and activation will be performed utilizing established methods. Mutational analysis of somatic changes in AR, MAPK, and PI3K pathway members will be performed by testing an aliquot of tumor DNA. Mutations will be identified in baseline tumor tissue. Cases will be classified as mutation positive or negative for each gene, and the location and type of each mutation will be documented. If mutations are observed, then an aliquot of normal DNA will be tested to determine if the mutation is somatic or not as this study will focus on confirmed somatic mutations.

In terms of RNA, we will perform the spatial RNA sequencing using Visium platform to characterize the spatial topography of transcriptomic expression. Spatial transcriptomics is a powerful technology for molecular profiling analysis that allows us to not only to identify all the gene activity in a tissue sample and map where the activity is occurring, but also to promote the understanding of complexity of transcriptional landscapes within a spatial context, which is needed for the understanding of biology and complex disease. The frozen tissue from pre-treatment and post-treatment will be fixed and permeabilized to release RNA which binds to adjacent capture probes, allowing for the capture of gene expression information. cDNA will be then synthesized from captured RNA and sequencing libraries will be prepared. This assay will be performed under Dr. Sood's laboratory at MD Anderson and in collaboration with Genomic and RNA Profiling Core at Baylor College of Medicine (Houston, TX).

We will also perform mass spectrometry (MS) based proteomics and phosphoproteomics in collaboration with Inova Fairfax Hospital (Falls Church, VA). MS-based proteomics analysis is the most comprehensive assays to measure the quantitative protein profiling of proteins, and their protein-protein networks and interactions. In brief, tumor cells from frozen tissues will be harvested by laser miscrodissection. The processed samples will be analyzed using a microscaled tandem mass tag (TMT)-mass spectrometry (MS) -based proteomic/phosphoproteomic workflow.

Reverse phase protein lysate array (RPPA) is a high throughput, functional proteomics tool that can quantify protein expression in a target, as well as, others in pathways of interest, simultaneously, and from small aliquots of tissue. RPPA requires only nanograms of protein lysate to measure total protein levels, phosphorylation, apoptosis, and cell-cycle progression. We have performed RPPA analysis on over 500 endometrial cancer allowing us to identify correlations with AR expression in endometrial

cancer that can provide potential biomarkers of activity of enzalutamide. It is important to note that both response elements and proteins coordinately expressed in the same lineage will be identified. In addition, these proteins could also serve as resistance markers due to co-expression. Based on this analysis, we propose to perform RPPA on each sample to identify potential biomarkers that predict response to enzalutamide as well as to identify potential biomarkers of pharmacodynamic activity. RPPA has been successfully used for this process in a number of patient and drug studies. In terms of potential response elements, we will emphasize GATA and FOXO family members, IGFBP2, INPP4B and FASN as key response elements, ER and phosphoER due to cross talk, and cell surface receptors and the PI3K pathway as known resistance markers. In terms of DNA, we will perform our T200.1 analysis which covers the spectrum of mutations present across tumors in the actionable cancer genome, any genomic event identified in more than 3% of cancers and comprehensive high resolution whole genome copy number analysis. The studies of signaling in tumor tissues could potentially show differential effects if access to tumor and normal tissue by drug is different or if there are context-dependent effects in tumor cells related to genomic anomalies. The comparative studies will also reveal whether tumor cells have increased sensitivity to enzalutamide such as increased apoptosis, as a result of addiction to the AR pathway or increased uptake by tumor cells.

Tumor expression of PTEN will be evaluated in the MDACC clinical lab. The PTEN assay is highly validated. Immunostaining for PTEN will be evaluated in nuclei and cytoplasm using a validated immunohistochemistry assay in standard fashion and results scored as follows. Complete absence of staining in the tumor cells in the presence of internal positive control (stromal cells, lymphocytes) will be interpreted as PTEN loss. Cases will be scored as being PTEN positive or retained if all or majority of the tumor shows positive staining. Cases with patchy PTEN staining will be interpreted as showing mixed staining.

Additionally, Cyclic immunohistochemistry (CycIHC) and/or Cyclic immunofluorescence (CycIF)- a powerful approach by multiplex imaging techniques samples will be performed using FFPE in order to investigate major signaling pathways, PI3K and RAS/RAF/MEK i.e. as well as tumor microenvironment and architectural patterns under the supervision of Dr. Mills laboratory at Oregon Health & Science University (OHSU).

9.0 STUDY CALENDARS

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done within 4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 2 days prior to initiation of the next cycle of therapy. All assessments can be performed ±7 days from the noted time point unless another specific timeframe is indicated.

9.1 Safety Lead-in Study Calendar (Part A)

		Cycle 1			Cycle 2			Cycle 3+[h]			
	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Off Study [i]
Enzalutamide[a]		X----------X			X----------X			X----------→			
Paclitaxel		X			X			X			
Carboplatin		X			X			X			
Informed consent	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	X	X	X	X			X			
Physical exam	X	X	X	X	X			X			X
Vital signs	X	X	X	X	X			X			X
Height	X										
Weight	X	X	X	X	X			X			X
PT, PTT, INR	X										
Performance Status	X	X			X			X			X
CBC w/diff, platelets[b]	X	X	X	X	X			X			X
Serum chemistry[c]	X	X	X	X	X			X			X
LVEF (ECHO)	X										
EKG	X	As clinically indicated									
Adverse event eval.		X----------X									X
Radiologic evaluation	X									X[f]	X[g]
B-HCG	X[d]										
Blood for PKs					X[e]						

a. Dose as assigned.
b. Includes platelets, Absolute neutrophil count, and hemoglobin
c. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphorus, potassium, total protein, AST, ALT, sodium.
d. Serum pregnancy test (women of childbearing potential).
e. PK samples to be collected from the first 20 patients on Safety Lead-in and Phase II: See Appendix B for details and timing. Patients will be instructed to bring their daily dose of Enzalutamide to CTRC to be taken in the presence of a nurse at the appropriate time for PK blood collections.
f. Tumor measurements (radiologic evaluation) to be performed every 9 weeks.
g. Off-study evaluation: Patients off therapy and on surveillance will have radiographical assessment performed every 3 months with their visits for 1 year. Thereafter, they will have imaging based on clinical parameters.
h. Maximum of 9 cycles.

9.2 Phase II Study Calendar (Part B)

		Cycle 0				Cycle 1			Cycle 2			Cycle 3+[i]			
	Pre-Study	Wk -4	Wk -3	Wk -2	Wk -1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Off Study
Enzalutamide[a]		X----------X				X----------X			X----------X			X----------→			
Paclitaxel						X			X			X			
Carboplatin						X			X			X			
Informed consent	X														
Demographics	X														
Medical history	X														
Concurrent meds	X	X				X			X			X			
Physical exam	X	X				X			X			X			X
Vital signs	X	X				X			X			X			X
Height	X	X													
Weight	X	X				X			X			X			X
PT, PTT, INR	X	As clinically indicated.													
Performance Status	X	X				X			X			X			X
CBC w/diff, platelets[b]	X	X				X			X			X			X
Serum chemistry[c]	X	X				X			X			X			X
LVEF (ECHO)	X														
EKG	X	As clinically indicated													
Adverse event eval.		X----------X													X
Radiologic evaluation	X													X[g]	X[h]
B-HCG	X[d]														
Tumor Biopsy	X				X[e]										
Blood for PKs									X[f]						
Blood for Biomarkers and DNA-sequencing	X				X[e,j]										

a. Dose as assigned.
b. Includes platelets, Absolute neutrophil count, and hemoglobin
c. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphorus, potassium, total protein, AST, ALT, sodium.
d. Serum pregnancy test (women of childbearing potential).
e. Preferably obtained Days 26-28.
f. PK samples to be collected from the first 20 patients on Safety Lead-in and Phase II: See Appendix B for details and timing. Patients will be instructed to bring their daily dose of Enzalutamide to CTRC to be taken in the presence of a nurse at the appropriate time for PK blood collections.
g. Tumor measurements (radiologic evaluation) to be performed every 9 weeks.
h. Off-study evaluation: Patients off therapy and on surveillance will have radiographical assessment performed every 3 months with their visits for 1 year. Thereafter, they will have imaging based on clinical parameters.
i. Maximum of 10 cycles (including Cycle 0).
j. Patient blood will only be collected for DNA-sequencing at Week -1 if it was not already collected pre-treatment

10.0 MEASUREMENT OF EFFECT

10.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 9 weeks once combination therapy starts. In addition to a baseline scan, confirmatory scans should also be obtained 9 weeks following initial documentation of objective response. For the purposes of this study Spiral CT or MRI are acceptable methods to evaluate target lesions. It is recommended that the same imaging modality be utilized during the study for consistency.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[22]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

10.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with enzalutamide. Toxicity will be assessed for both single-agent enzalutamide (Cycle 0) and for subsequent cycles where combination therapy will be administered.

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

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

10.1.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area need biopsy confirmation of active disease before being considered measurable.

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

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

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

10.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before 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 unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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

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

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly

impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

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

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published[23]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer[23].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

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

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

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

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

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

10.1.4 Response Criteria

10.1.4.1 Evaluation of Target Lesions

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

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

10.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally

trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

10.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

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

** Only for non-randomized trials with response as primary endpoint.

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

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

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* '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 so to assign this category when no lesions can be measured is not advised		

10.1.5 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 recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive 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, including the baseline measurements.

10.1.6 Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. Patients without progression or death will be censored on the date of last response assessment.

10.1.7 Overall Survival (OS)

OS is defined as the duration of time from start of treatment to time of death. Patients alive will be censored on the date of last contact.

11.0 DATA REPORTING/REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 6.0 (Adverse Events: List and Reporting Requirements).

11.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by the IRB, Astellas, and the NCCN. Any changes made to the

protocol must be submitted as amendments and must be approved by the IRB, Astellas, and the NCCN prior to implementation. Any changes in study conduct must be reported to the IRB, Astellas, and the NCCN.

11.2 Safety Review Meetings

Biweekly safety review meetings/telephone conferences will be held to discuss dose-limiting toxicities and significance, serious adverse events, and study progress during safety lead in. Meeting invitees will include the study PI, co-PI, study nurse, and data coordinators.

11.3 Toxicity Summaries

During the lead in phase/Part A, submit a toxicity summary to the IND Medical Monitor after 3 subjects are evaluable, prior to dose de-escalation or dose expansion. During Phase II/Part B, submit a toxicity/efficacy summary after the first 10 subjects are evaluable for toxicity and response and every 5 subjects thereafter.

11.4 Data Entry

All data will be entered into the Prometheus Software Platform. Prometheus is a secure portal that requires users to login with validated credentials, has granular data access controls to ensure that the minimal amount of information required to complete a task is presented, handles the de-linking and de-identification of patient information to maintain patient confidentiality. Prometheus provides a multi-institute 21 CFR 11 compliant data capture portal to simplify these tasks. Standard data collection, storage procedures, and quality assurance procedures will be followed to ensure integrity and auditability of all information entered

12.0 STATISTICAL CONSIDERATIONS

Summary statistics will be used to describe the demographic and clinical characteristics of patients. Patient groups evaluable for response and for toxicity are defined above in section 10.

12.1 Study Design/Endpoints

Primary Endpoints:

1. Efficacy of combination - defined by objective response rate (RR = CR +PR) and % of patients surviving progression free at 6 months.

2. Molecular aberrations as discussed in correlative section, including but not limited to, AR receptor expression and activation, expression of AR-related genes, sequencing of AR-related pathway members.

3. Rate of toxicity, defined by dose-limiting toxicities experienced during safety lead in and feasibility, defined as % of patients that receive three cycles of chemotherapy.

Secondary Endpoints:

1. Response Duration
2. Progression free survival and overall survival.
3. Pharmacokinetic parameters including, but not limited to, Tss, Css, Cmax.

12.2 Analysis

Summary statistics and boxplots will be used to describe the distributions of expression of AR and its downstream signaling effectors. We will similarly describe the change from baseline for AR and its downstream signaling effectors. If the usual normality assumptions hold we will use a paired t-test to test for significant changes in expression from baseline to follow-up assessment, otherwise we will test for changes with the Wilcoxon signed-rank test. For those variables measured on a nominal scale we will cross-tabulate values at baseline and follow-up assessments, and we will test for differences between baseline and follow-up assessments with a Fisher's exact test. We will use Cox[24] proportional hazards regression to model PFS and OS as functions of mutation status and protein expression, and we will estimate hazard ratios with 95% confidence intervals. A time dependent covariate analysis may be conducted to assess the impact of changes in biomarker expression on PFS and OS.

Toxicity: We will monitor the rate of DLT during cycle 1 of therapy using the Bayesian optimal phase II (BOP2) method of Zhou, et al[25]. Specifically, let n denote the interim sample size and N denote the maximum sample size. Let p_{tox} denote the probability of toxicity. We will stop enrolling patients and inspect the safety data for possible trial termination if

$$\boldsymbol{Pr(p_{tox} \leq 0.4|data) < \lambda(\frac{n}{N})^{\alpha}},$$

where λ=0.75 and α=0.7 are design parameters optimized to minimize the chance of incorrectly claiming that a safe treatment is unacceptable under the alternative hypothesis $H_1: p_{tox} = 0.2$, while controlling the type I error rate at 0.2 under the null hypothesis $H_0: p_{tox} > 0.4$, representing that toxicity is unacceptably high. (i.e., the chance of incorrectly claiming that an overly toxic treatment is acceptable is no more than 20%). Assuming a Beta(0.4,0.6) prior distribution for p_{tox}, the above decision rule corresponds to the following stopping boundaries:

Table 5: Optimized stopping boundaries

# patients treated	Stop if DLT >=
10	6
20	9
30	12
45	16

Based on Table 5, we perform the interim analysis when the number of enrolled patients reaches 10, 20, 30. When the total number of patients reaches the maximum sample size of 45, we reject the null hypothesis and conclude that the treatment is acceptable if the number of toxicities are less than 16; otherwise we conclude that the treatment is unacceptable.

Below are the operating characteristics of the design based on 10000 simulations using the BOP2 web application, which is available at http://www.trialdesign.org.

Table 6: Operating characteristics of toxicity monitoring

Toxicity rate	Early stopping (%)	Claim acceptable (%)	Sample size
0.2	1.84	97.67	44.5
0.3	20.36	69.33	40.2
0.4	60.65	19.68	30.0
0.5	91.62	1.25	19.9

Efficacy: Our primary outcomes are objective tumor response (OR, including CR/PR) rate (ORR) and PFS at 6 months (PFS6). We will use the Bayesian optimal phase II (BOP2) design of Zhou, et al[25] to conduct the study in 2 stages and test the following hypothesis:

H_0: $\pi_r \leq 50\%$ and $\pi_s \leq 40\%$ where π_r is the true ORR and π_s is the true proportion of patients with PFS > 6 months. We will stop enrolling patients and claim the treatment is not promising if

$$\mathbf{Pr}\,(\boldsymbol{\pi_r} > \mathbf{0.5}|\boldsymbol{data}) < \boldsymbol{\lambda}(\frac{\boldsymbol{n}}{\boldsymbol{N}})^{\boldsymbol{\alpha}},$$

AND

$$\mathbf{Pr}\,(\boldsymbol{\pi_s} > \mathbf{0.4}|\boldsymbol{data}) < \boldsymbol{\lambda}(\frac{\boldsymbol{n}}{\boldsymbol{N}})^{\boldsymbol{\alpha}},$$

where λ=0.95 and α=0.2 are design parameters optimized to minimize the chance of incorrectly claiming that an efficacious treatment is not promising (i.e., type II error) under the alternative hypothesis H_1: π_r=70% and π_s=60%, which is considered clinically significant, while controlling the type I error rate at 0.1 (i.e., the chance of incorrectly claiming that an inefficacious treatment is promising is no more than 10%). Assuming a Dirichlet prior distribution $Dir(0.05,0.45,0.35,0.15)$ for the treatment effect, the above decision rule corresponds to the following stopping boundaries and yields a statistical power of 0.9448 under H_1:

Table 7: Optimized stopping boundaries

# patients treated	Stop if # of OR <=	AND	# of progression free at 6 months <=
20	11		9
45	27		23

Based on Table 7, we perform the interim analysis when the number of enrolled patients reaches 20. When the total number of patients reaches the maximum sample size of 45, we reject the null hypothesis and conclude that the treatment is promising if the number of responses in first endpoint are greater than 27, or the number of responses in second endpoint are greater than 23; otherwise we conclude that the treatment is not promising. We will estimate OS, PFS, and response duration using the Kaplan Meier method. We will tabulate toxicity, responses to therapy and estimate ORR with a 95% confidence interval.

Below are the operating characteristics of the design based on 10000 simulations using the BOP2 web application, which is available at http://www.trialdesign.org.

Table 8: Operating characteristics

ORR	PFS6	Pr(OR & PFS6)	Correlation OR & PFS6	Early stopping (%)	Claim promising (%)	Sample size
0.5	0.4	0.20	Independent	56.84	9.90	30.8
0.5	0.4	0.30	Positive	62.06	9.21	29.5
0.5	0.4	0.15	Negative	54.93	10.04	31.3
0.7	0.6	0.42	Independent	1.52	97.28	44.6
0.7	0.6	0.50	Positive	3.55	94.48	44.1
0.7	0.6	0.35	Negative	0.32	99.36	44.9
0.7	0.4	0.32	Positive	9.57	85.13	42.6
0.5	0.6	0.40	Positive	12.22	79.87	41.9

12.3 Sample Size/Accrual Rate

We assume that a particular biomarker will increase (or decrease) with probability 0.50 if there is no treatment effect. With 45 patients we will have 83% power with a 1-sided significance level of 0.05 to detect a probability of a particular biomarker's expression increasing (or decreasing) of 0.70 using an exact binomial test. Forty-five patients will also give us 90% power with a 2-sided significance level of 0.05 and a paired t-test to detect an effect size of 0.5 standard deviations (SD) for the change in biomarker expression from pre- to post-treatment. A sample of 20 patients will give us 80% power to detect a probability of a biomarker increasing (or decreasing) of 0.80 and 81% power to detect an effect size of 0.67 SD for the change in biomarker expression, should the study be stopped early. In addition, given the sample size of 45, the 95% confidence interval for the estimates of toxicity rate and the feasibility (i.e., the percent of patients that receive three cycles of chemotherapy) will not be wider than 0.29. No adjustment for multiple testing is made as these analyses are considered exploratory in nature. These sample size calculations were performed using nQuery Advisor ® 8.0 (Copyright © 1995-2007, Statistical Solutions, Saugus, MA).

12.4 Analysis of Secondary Endpoints and Exploratory Objectives

Response

We will use summary statistics to describe the duration of response (CR, CR+PR) and the duration of SD for patients with these responses.

PFS and OS

PFS and OS are defined above in section 10. We will estimate PFS and OS with the product-limit estimator of Kaplan and Meier and illustrate PFS and OS with Kaplan-Meier plots.

Toxicity

We will tabulate the adverse events by grade and relationship to study drug. Grading and reporting of adverse events is described above in section 6.

Correlation

Regression analysis will be used to correlate results, including AR receptor expression and activation, to clinical endpoints. Normal regression model will be used for continuous clinical endpoints, logistic

regression will be used for binary clinical endpoints, and Cox regression will be used for survival endpoints (e.g., PFS and OS). Standard model assessment methods (e.g., residual plots) will be used to assess the goodness of the fit of the models.

13.0 REFERENCES

[1] Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, Wongvipat J, Smith-Jones PM, Yoo D, Kwon A, Wasielewska T, Welsbie D, Chen CD, Higano CS, Beer TM, Hung DT, Scher HI, Jung ME, Sawyers CL: Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009, 324:787-90.

[2] Siegel RL, Miller KD, Jemal A: Cancer statistics, 2015. CA Cancer J Clin 2015, 65:5-29.

[3] Obel JC, Friberg G, Fleming GF: Chemotherapy in endometrial cancer. Clin Adv Hematol Oncol 2006, 4:459-68.

[4] Miller DS, Filiaci VJ, Fleming G, Mannel R, Cohn DE, Matsumoto T, Tewari K, DiSilvestro PA, Pearl M, Zaino RJ: Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. Gynecol Oncol 2012, 125:771.

[5] Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, Robertson AG, Pashtan I, Shen R, Benz CC, Yau C, Laird PW, Ding L, Zhang W, Mills GB, Kucherlapati R, Mardis ER, Levine DA: Integrated genomic characterization of endometrial carcinoma. Nature 2013, 497:67-73.

[6] Lentz SS, Brady MF, Major FJ, Reid GC, Soper JT: High-dose megestrol acetate in advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol 1996, 14:357-61.

[7] Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, Soper JT, Given FT: Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1999, 17:1736-44.

[8] Whitney CW, Brunetto VL, Zaino RJ, Lentz SS, Sorosky J, Armstrong DK, Lee RB, Gynecologic Oncology Group s: Phase II study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004, 92:4-9.

[9] Fiorica JV, Brunetto VL, Hanjani P, Lentz SS, Mannel R, Andersen W, Gynecologic Oncology Group s: Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004, 92:10-4.

[10] Rose PG, Brunetto VL, VanLe L, Bell J, Walker JL, Lee RB: A phase II trial of anastrozole in advanced recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2000, 78:212-6.

[11] Horie K, Takakura K, Imai K, Liao S, Mori T: Immunohistochemical localization of androgen receptor in the human endometrium, decidua, placenta and pathological conditions of the endometrium. Hum Reprod 1992, 7:1461-6.

[12] Ito FA, Ito K, Coletta RD, Vargas PA, Lopes MA: Immunohistochemical study of androgen, estrogen and progesterone receptors in salivary gland tumors. Brazilian oral research 2009, 23:393-8.

[13] Hackenberg R, Schulz KD: Androgen receptor mediated growth control of breast cancer and endometrial cancer modulated by antiandrogen- and androgen-like steroids. J Steroid Biochem Mol Biol 1996, 56:113-7.

[14] Liang S, Mu K, Wang Y, Zhou Z, Zhang J, Sheng Y, Zhang T: CyclinD1, a prominent prognostic marker for endometrial diseases. Diagnostic pathology 2013, 8:138.

[15] Lyu S, Yu Q, Ying G, Wang S, Wang Y, Zhang J, Niu Y: Androgen receptor decreases CMYC and KRAS expression by upregulating let-7a expression in ER-, PR-, AR+ breast cancer. Int J Oncol 2014, 44:229-37.

[16] Gibson DA, Simitsidellis I, Collins F, Saunders PT: Evidence of androgen action in endometrial and ovarian cancers. Endocr Relat Cancer 2014, 21:T203-18.

[17] Yang HP, Gonzalez Bosquet J, Li Q, Platz EA, Brinton LA, Sherman ME, Lacey JV, Jr., Gaudet MM, Burdette LA, Figueroa JD, Ciampa JG, Lissowska J, Peplonska B, Chanock SJ, Garcia-Closas M: Common genetic variation in the sex hormone metabolic pathway and endometrial cancer risk: pathway-based evaluation of candidate genes. Carcinogenesis 2010, 31:827-33.

[18] Lochrin SE, Figg WD, 2nd, Finn SP: Enzalutamide for treatment of CRPC: rationale for sequencing and potential clinical biomarker for resistance. Cancer Biol Ther 2015, 16:201-3.

[19] Burgio SL, Conteduca V, Menna C, Carretta E, Rossi L, Bianchi E, Kopf B, Fabbri F, Amadori D, De Giorgi U: Chromogranin A predicts outcome in prostate cancer patients treated with abiraterone. Endocr Relat Cancer 2014, 21:487-93.

[20] Hennessy BT, Lu Y, Poradosu E, Yu Q, Yu S, Hall H, Carey MS, Ravoori M, Gonzalez-Angulo AM, Birch R, Henderson IC, Kundra V, Mills GB: Pharmacodynamic markers of perifosine efficacy. Clin Cancer Res 2007, 13:7421-31.

[21] Sheehan KM, Calvert VS, Kay EW, Lu Y, Fishman D, Espina V, Aquino J, Speer R, Araujo R, Mills GB, Liotta LA, Petricoin EF, 3rd, Wulfkuhle JD: Use of reverse phase protein microarrays and reference standard development for molecular network analysis of metastatic ovarian carcinoma. Mol Cell Proteomics 2005, 4:346-55.

[22] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009, 45:228-47.

[23] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000, 92:205-16.

[24] Cox DR: Regression models and life tables (with discussion). Journal of the Royal Statistical Society B 1972, 34:187-220.

[25] Zhou H, Lee JJ, Yuan Y: BOP2: Bayesian optimal designs for phase II clinical trials with simple and complex endpoints. Stat Med 2017, 36:3302-14.

APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. 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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: PHARMACOKINETIC SCHEDULE

PHARMACOKINETIC EVALUATIONS SCHEDULE
(To occur on Cycle 2, Day 1)

Time of Blood Draw	PK for Enzalutamide	PK for Paclitaxel
Prior to Paclitaxel dosing (within 1 hr prior to paclitaxel infusion)	X[a]	
30 min (± 2 min) from **START** of paclitaxel infusion	X	
1 h (± 10 min) from **START** of paclitaxel Infusion	X	
2 h (± 10 min) from **START** of paclitaxel Infusion	X	
15 min (± 2 min) after **END** of paclitaxel infusion[b]		X
30 min (± 2 min) after **END** of paclitaxel infusion		X
1 h (± 10 min) after **END** of paclitaxel Infusion	X	
2 h (± 10 min) after **END** of paclitaxel Infusion		X
4 h(± 10 min) after **END** of paclitaxel Infusion		X

a. Only one tube needs to be collected, and this sample will be used as baseline for Enzalutamide and Paclitaxel.

b. Infusion time of paclitaxel is 3 hours. Carboplatin infusion can be started as per standard practice. The timing of blood draws for PKs should be collected based on the paclitaxel infusion time and not the carboplatin infusion time.

APPENDIX C: Patient Medication Diary – CYCLE 0 (28 Days)

PATIENT'S MEDICATION DIARY – Enzalutamide

Today's date _____ **Agent enzalutamide**

Patient Name_____ (*initials acceptable*) **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

Complete one form every 3 weeks (one treatment cycle).

You will take your enzalutamide tablets each day in the morning. You will take ___ 40 mg capsules per day. You may take enzalutamide with or without food, as you wish.

Record the date, the number of tablets of each size you took, and when you took them.

If you have any comments or notice any side effects, please record them in the Comments column.

Please bring this form and your bottles of enzalutamide capsules when you return for each appointment.

Day	Date			Time of morning dose		# of tablets taken	Comments
						40mg	
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							

Day	Date			Time of morning dose		# of tablets taken		Comments
						40 mg		
14								
15								
16								
17								
18								
19								
20								
21								
22								
23								
24								
25								
26								
27								
28								

Patient's signature _____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of tablets taken this month (each size)_____
5. Physician/Nurse/Data Manager's Signature _____

APPENDIX D: Patient Medication Diary – Cycle 1+ (21 Days)

PATIENT'S MEDICATION DIARY – Enzalutamide

Today's date _____ **Agent enzalutamide**

Patient Name_____ (*initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

Complete one form every 3 weeks (one treatment cycle).

You will take your enzalutamide tablets each day in the morning. You will take ___ 40 mg capsules per day. You may take enzalutamide with or without food, as you wish.

Record the date, the number of tablets of each size you took, and when you took them.

If you have any comments or notice any side effects, please record them in the Comments column.

Please bring this form and your bottles of enzalutamide capsules when you return for each appointment.

Day	Date			Time of morning dose		# of tablets taken	Comments
						40mg	
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							

Day	Date	Time of morning dose	# of tablets taken	Comments
			40 mg	
13				
14				
15				
16				
17				
18				
19				
20				
21				

Patient's signature _____

Physician's Office will complete this section:

1. Date patient started protocol treatment _____
2. Date patient was removed from study _____
3. Patient's planned total daily dose _____
4. Total number of tablets taken this month (each size) _____
5. Physician/Nurse/Data Manager's Signature _____

APPENDIX E: Substrates, Inhibitors, or Inducers of CYP3A4, CYP2C8, CYP2C9 or CYP2C19

Due to the dynamic nature of this list, we will refer to the up-to-date list found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. To ensure the link is working properly, it will be tested at least every other month if not used to check a patient's concomitant medicines during the study within 60 days.

If at any time the link is not working, the most recently cached version of the website will be utilized, and then the protocol will be revised to insert an updated link or physical version of the list as necessary. The cached version of the table will be found by searching via "google.com" for the search term "iupui flockhart table" and selecting the cached version from the results.