Local Protocol #: IRB16-0403; NCT#: NCT02788981

TITLE: "A Randomized, Placebo-Controlled, Double-Blind, Phase II Trial of Nanoparticle Albumin-bound Paclitaxel (nab-paclitaxel, Abraxane®) with or without Mifepristone for Advanced, Glucocorticoid Receptor-Positive, Triple-Negative Breast Cancer".

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This study is being conducted by institutional members of the Personalized Cancer Care Consortium (PCCC) as well as additional non-PCCC sites.

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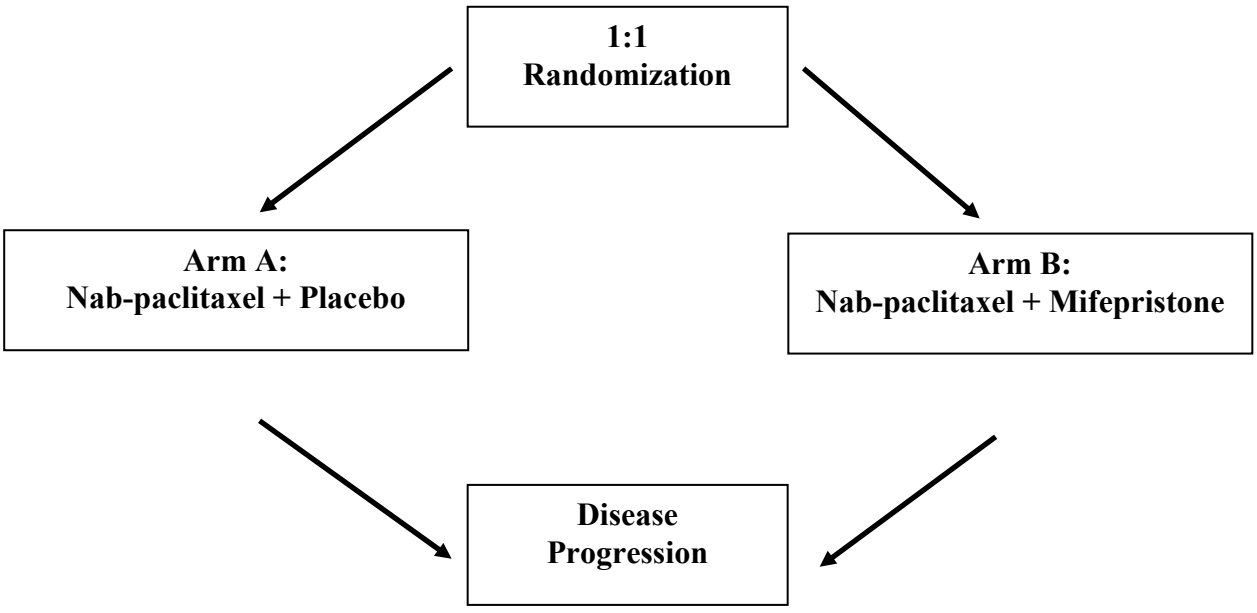
This is a randomized, placebo-controlled, double-blind, phase II trial of nab-paclitaxel with or without mifepristone for advanced, triple-negative breast cancer. A total of 72 patients will receive nab-paclitaxel 100 mg/m2 on days 1, 8 and 15 of each 28 day cycle: patients will be randomly assigned to either receive placebo (n=36 patients) or to receive mifepristone 300 mg daily on the day prior to and day of each dose of nab-paclitaxel (n=36 patients). Patients will be enrolled over 24 months and followed for 12 months following completion of study. The primary endpoint will be to compare the progression- free survival (PFS) of patients treated with nab-paclitaxel plus mifepristone versus patients treated with nab-paclitaxel plus placebo.

To expand and follow up on our understanding of a potential PK interaction between nab-paclitaxel and mifepristone, we will perform PK studies in the first 20 patients enrolled at pre-specified "PK sites". Patients in this portion of the study will have paclitaxel levels drawn at pre-specified time points (at baseline, and then 15 mins, 45 mins, 4 hrs, 6 hrs, and 24 hrs after the end of nab-paclitaxel infusion). These patients will not receive mifepristone or placebo week one; mifepristone or placebo will start week two. Paclitaxel levels will be drawn cycle1/day1-2 and cycle1/day8-9. PK results will not be required to proceed with the study and will not be performed in real time.

	Day (of 28 day cycle)					
Treatment	**0**	**1**	**7**	**8**	**14**	**15**
nab-paclitaxel		X		X		X
Mifepristone*	X	X	X	X	X	X

*Patients enrolled on PK portion of study will not receive mifepristone or placebo week one; mifepristone or placebo will start week two.



SCHEMA

Key Patient Eligibility (for full list refer to Section 3)	Required Laboratory Data	
Metastatic or locally advanced breast cancer not amenable to local therapy. Triple negative breast cancer (defined as ER and PR <10% positive; HER2 0-1+ by IHC or FISH ratio < 2.0) Measurable disease. ECOG PS 0-2. Age ≥ 18 years. Non-pregnant and not breast feeding. Up to two prior cytotoxic therapies for metastatic disease. No prior therapy with nab-paclitaxel for metastatic disease. Patients with brain metastases will be eligible provided brain metastases have been treated and steroids have been discontinued for at least 7 days. No currently active secondary malignancy. Peripheral neuropathy < grade 2. No other serious medical or psychiatric disease. No serious active infection (viral, fungal, bacterial). No infection requiring parenteral antibiotics at the time of registration. No long term or concurrent use of corticosteroid therapy	Absolute neutrophils Platelets Hemoglobin Bilirubin AST and ALT (if liver mets present Alkaline phosphatase (if bone mets present Creatinine (Cr) Cr clearance (if Cr above ULN) INR	≥ 1,500/uL ≥ 100,000/uL > 9.0 g/dL ≤ 1.5 mg/dL ≤ 2.5 ULN* ≤ 5 X ULN) ≤ 2.5 X ULN ≤ 5 X ULN) ≤ ULN ≥ 60 mL/min/1.73m2 ≤ 1.5

* ULN = upper limit of normal

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1. OBJECTIVES

1.1 Primary Objective

Progression-free survival (PFS): To compare the progression free survival (PFS) of patients with GR-positive, triple-negative breast cancer treated with nab-paclitaxel + placebo and patients treated with nab-paclitaxel + mifepristone

1.2 Secondary Objectives

1.2.1 To correlate percentage glucocorticoid receptor (GR) positivity in the most recent metastatic tumor biopsy (or in primary tumor if only primary tumor is available) with PFS in mifepristone and placebo groups of patients with GR-positive, triple-negative breast cancer

1.2.2 To perform an exploratory assessment of overall response rate in both groups of patients with GR-positive, triple-negative breast cancer

1.2.3 To collect information regarding overall survival in both treatment cohorts of patients with GR-positive, triple-negative breast cancer

1.3 Exploratory Objectives

To expand on our understanding of the interaction between nab-paclitaxel and mifepristone by performing PK studies in the first 20 patients enrolled at pre-specified PK sites.

2. BACKGROUND

2.1 Breast Cancer

Breast cancer is the second highest cause of cancer death in women in the United States[1]. While breast cancer is being diagnosed at earlier stages because of mammography, approximately 20-30% of patients go on to develop distant metastases, and about 6-10% of women in the U.S. present with metastatic disease. Chemotherapy and hormone therapy have both been used in the treatment of metastatic disease. Most patients initially experience an objective response, with responses lasting anywhere from 8-14 months. Unfortunately, progression of disease is inevitable, and response to second-line therapy is less likely less durable [2].

2.2 Nab-paclitaxel (Abraxane) and breast cancer

Paclitaxel is a taxane derivative that is among the most active agents in the treatment of breast cancer. Paclitaxel inhibits mitosis and leads to cell death by binding to dimeric tubulin and causing disruption of microtubule disassembly. Response rates in taxane naïve patients with metastatic breast cancer have ranged from 20-60%. Several studies have been conducted investigating the optimal dose and schedule of paclitaxel delivery. Weekly therapy appears to be more efficacious and has less hematologic toxicity than every three week dosing [3].

One major limitation of paclitaxel is its poor water solubility. Due to poor solubility, paclitaxel must be dissolved in the solvent Cremophor EL and in relatively large volumes of fluid and administered over a 1-3 hour time period. Cremophor EL is associated with many side effects, including anaphylaxis, and thus requires premedication with both corticosteroids and antihistamines[4].

Nab-paclitaxel is an albumin-bound, solvent-free novel formulation of the insoluble drug paclitaxel that eliminates the need for pre-medications, including steroid premedication, and the risk of hypersensitivity from the paclitaxel solvent. The nanoparticles are stable in liquid suspensions and suitable for injection. This composition increases intra-tumoral concentrations of the drug by a receptor-mediated transport process allowing transcytosis across the endothelial cell wall, thus breaching the blood/tumor interface[5]. The maximum tolerated dose (MTD) in heavily pretreated patients was 100 mg/m^2, given weekly for 3 weeks out of every 4 week cycle. A large phase II study evaluating weekly nab-paclitaxel demonstrated response rates of 14-16% in taxane-resistant, pre-treated metastatic breast cancer patients. Nab-paclitaxel was well tolerated when administered weekly over 30 minutes without steroids or growth factor support [6].

2.3 Mifepristone

Glucocorticoid receptor and breast cancer

The glucocorticoid receptor (GR) is expressed in a significant subset of both ER alpha-positive and -negative human breast cancers.[7]. *In vitro* and *in vivo* experiments suggest that activation of the GR in ER-negative pre-malignant breast epithelial and cancer cells initiates cell survival pathways under otherwise apoptosis-inducing conditions (e.g. chemotherapy, radiation, and growth factor deprivation). Thus, GR antagonism is predicted to enhance chemotherapy sensitivity of GR+/ER- breast cancer cells by blocking stress-mediated cell survival pathways that would otherwise counteract chemotherapy-induced apoptosis in tumor cells [8].

In support of the hypothesis that GR activation via endogenous stress hormones mediates chemo-resistance (and associated increase risk of relapse for early stage ER- breast cancers), we recently examined the association between the levels of GR (NR3C1) gene expression and the pattern of GR target gene expression in human ER- breast cancers and cell lines. We found that in ER- early stage breast cancers, high GR expression in the primary tumor is associated with a significantly increased probability of relapse[9] This was not observed in ER+ early stage tumors. This analysis and previous data in breast and ovarian cancer have led to the hypothesis that “GR high” breast tumors demonstrate increased chemo-resistance through GR-mediated anti-apoptotic signaling and would be predicted to show an improved response to cytotoxic therapies if GR antagonist therapy is administered prior to chemotherapy [10]. Further data from the Conzen laboratory showed co-treatment with the GR-antagonist mifepristone both reverses GR-mediated gene expression in 3 TNBC cell lines and augments chemotherapy induced apoptosis [11].

Mifepristone

Mifepristone is a progesterone and glucocorticoid receptor antagonist currently FDA approved

for termination of early pregnancy and the treatment of Cushing's syndrome. It is also known to be a potent inhibitor of the GR[12]. Animal studies suggest that GR antagonism may be of value in the treatment of a variety of diseases such as glucocorticoid-dependent hypertension, arthritis, glaucoma, psychosis, addiction, and breast cancer [8, 12].

Cognition is adversely affected by high and sustained levels of glucocorticoids. In one small study, nine patients with mild to moderate Alzheimer's disease, patients were treated with either mifepristone 200 mg per day or placebo for six weeks. The mifepristone-treated patients performed better on the cognitive subtest of the Alzheimer's disease assessment scale, although the difference between patients treated with mifepristone and patients treated with placebo did not reach statistical significance [14, 15].

Many patients with psychotic depression have non-suppression of cortisol following dexamethasone administration. In addition, they can have increased urinary cortisol and increased serum ACTH levels. In one study of 30 patients with clinical depression, patients were randomly assigned to receive 50 mg, 600 mg or 1200 mg of mifepristone daily for seven days. Patients who received the higher two doses showed an improvement in symptomatology [16].

Since high cortisol levels have also been found in bipolar disorder, treatment with mifepristone has been explored as a potential therapy. In a study of 20 bipolar patients treated with either 600 mg/day or placebo, those patients who received mifepristone had selective improvements in neurocognitive function, including memory performance, verbal fluency, spatial recognition and mood[18]. Mifepristone, however, has not been shown to be of any benefit for the management of schizophrenia [19]

Several small single agent studies of mifepristone and another progesterone antagonist, onapristone, have been evaluated for the treatment of advanced breast cancer, with disappointing results [20-23]. However, these studies have been focused on the use of mifepristone as a PR antagonist.

Mifepristone is a specific progesterone receptor and glucocorticoid receptor antagonist, with rare unexpected adverse effects, even at doses as high as 1200 mg. Common side effects of long term treatment with doses of up to 200 mg include fatigue, nausea, rash, cessation of menses in premenopausal women and hot flashes [24-26]. Hypothyroidism has rarely been observed with long term use, and is likely related to the antiglucocorticoid effect that inhibits iodine uptake induced by hydrocortisone and TSH [27, 28]. Low serum potassium has also been reported in breast cancer patients on long-term daily doses of 200 mg day and Cushing's syndrome patients receiving up to 2000 mg daily [21, 29]. Overall, mifepristone is well tolerated, and most side effects are associated with continuous use of over 200 mg daily.

2.4 Rationale

Nab-paclitaxel is a relatively effective and well tolerated therapy for MBC. Unfortunately, many tumors do not respond, and those that do eventually develop resistance, so improved approaches for increasing tumor sensitivity to taxanes are needed. Glucocorticoid-mediated GR activation mediates tumor cell resistance by anti-apoptotic signaling. We hypothesize that

GR antagonism with mifepristone prior to the administration of cytotoxic chemotherapy will improve the efficacy of nab-paclitaxel by blocking the strong anti-apoptotic signal mediated by GR activation via circulating endogenous cortisol levels.

We have previously performed a phase I study of nab-paclitaxel and mifepristone. We studied two doses of nab-paclitaxel (100 mg/m^2 and 80 mg/m^2) in combination with mifepristone (300 mg) the day prior to and the morning of nab-paclitaxel infusion. Nab-paclitaxel was administered on days 1, 8, and 15 of a 28 day cycle and mifepristone was administered on days 0, 1, 7, 8, 14, and 15 of a 28 day cycle. Neutropenia occurred in many patients at both nab-paclitaxel dose levels studied, but was easily managed with dose reduction and/or growth factor administration. Additionally, promising efficacy was observed in patients with GR positive TNBC, with 4 of 6 patients having a response to therapy (2 complete responses, 2 partial responses, 1 stable disease, 1 progressive disease). Based on this promising efficacy we are proposing this randomized phase II study.

2.5 Correlative Studies Background

2.5.1 Pharmacokinetic Studies

CYP2C8 activity is known to be inhibited by mifepristone. CYP2C8 is also known to be involved in the metabolism of paclitaxel (and therefore nab-paclitaxel). It is therefore possible that paclitaxel levels may be increased with concomitant mifepristone administration.

To expand our understanding of a potential PK interaction between nab-paclitaxel and mifepristone, we will perform PK studies in the first 20 patients enrolled at pre-specified "PK collecting sites" in the beginning of this randomized phase II trial. Patients in this portion of the study will have paclitaxel levels drawn at pre-specified time points (at baseline, and then 15 mins, 45 mins, 4 hrs, 6 hrs, and 24 hrs after completion of nab-paclitaxel administration). These patients will not receive mifepristone or placebo week one; mifepristone or placebo will start week two. Paclitaxel levels will be drawn cycle 1/day 1 and cycle 1/day 8. PK results will not be required to proceed with the study and assays will not be performed in real time.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed breast cancer with stage IV or unresectable stage III disease.

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam. 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). See Section 11 for the evaluation of measurable disease.

3.1.3 Triple-negative breast cancer (defined as ER and PR <10% positive; HER2 0-1+ by IHC or FISH ratio < 2.0)

3.1.4 Patients may have received adjuvant chemotherapy and up to two prior chemotherapy for metastatic or locally recurrent disease. No prior nab-paclitaxel will be allowed. Prior mifepristone will be allowed.

3.1.5 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of Nab-Paclitaxel in combination with Mifepristone in patients < 18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.6 ECOG performance status ≤ 2 (Karnofsky ≥ 60%, see Appendix A).

3.1.7 Patients must have normal organ and marrow function as defined below

– absolute neutrophil count	≥ 1,500 cells/$mm^{3.}$
– platelets	≥ 100,000/mcL
– hemoglobin	> 9.0 g/dL
– total bilirubin*	≤ 1.5 mg/dL
– alkaline phosphatase	≤ 2.5 X ULN ≤ 5 X ULN if bone mets are present
– AST and ALT	≤ 2.5 ULN ≤ 5 X ULN if liver mets are present
– adequate renal function	creatinine ≤ institutional upper limit of normal OR creatinine clearance ≥ 60 mL/min/1.73 m2 for patients with creatinine levels above institutional normal.
– INR	≤ 1.5

*for patients with Gilbert's Syndrome, elevated total bilirubin is acceptable provided conjugated bilirubin is ≤ 1.5 X ULN

3.1.8 Females of child-bearing potential (defined as a sexually mature woman who (1) has not undergone hysterectomy [the surgical removal of the uterus] or bilateral oophorectomy [the surgical removal of both ovaries] or (2) has not been naturally postmenopausal for at least 24 consecutive months [i.e., has had menses at any time during the preceding 24 consecutive months]) must:

Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis), or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting IP therapy (including dose interruptions), and while on study medication or for a longer period if required by local regulations following the last dose of IP; and

Have a negative serum pregnancy test (β -hCG) result at screening and agree to ongoing pregnancy testing during the course of the study, and after the end of study therapy. This applies even if the subject practices true abstinence* from heterosexual contact.

3.1.9 Male subjects must practice true abstinence* or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for 6 months following protocol discontinuation, even if he has undergone a successful vasectomy. * True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].

3.1.10 Patients must have < Grade 2 pre-existing peripheral neuropathy (per CTCAE).

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who are receiving any other investigational agents.

3.2.2 Patients who have had chemotherapy or radiotherapy within 2 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.3 Patients with a “currently active” second malignancy other than non-melanoma skin cancers. Patients are not considered to have a “currently active” malignancy if they have completed therapy and are free of disease for ≥ 3 years.

3.2.4 Patients with known brain metastases will be eligible as long as they have completed radiation to the brain, and have been off of corticosteroid therapy for at least 7 days.

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to mifepristone or paclitaxel/nab-paclitaxel. Patients with a history of mild infusion reactions with paclitaxel who were able to continue to receive paclitaxel with corticosteroid premedication will be eligible to participate, as these cases were likely related to cremaphor and not paclitaxel.

3.2.6 Mifepristone can both inhibit CYP3A4 and induce CYP3A4. Addition of mifepristone to a pre-existing drug regimen may cause a mild and temporary increase in plasma drug concentration of drugs with significant CYP3A4 metabolism. Medications that are strong inducers of CYP3A4 such as carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentine, St. John's Wort may decrease plasma mifepristone levels. Strong CYP3A4 inhibitor medications are expected to cause the largest increases in plasma mifepristone concentrations.

Mifepristone may increase the plasma drug concentration of concomitant medications with metabolism mediated by CYP2C9/CYP2C8. Drugs with the largest increases will be those whose metabolism is largely or solely mediated by CYP2C9/2C8 and include: Non-steroidal Anti-inflammatory drugs (NSAIDs) and warfarin.

For a complete list of concomitant medication restrictions, please see Appendix C.

3.2.7 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Pregnant women are excluded from this study because mifepristone is an abortifacient agent with the potential for teratogenic effects.

3.2.9 Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with mifepristone, breastfeeding should be discontinued if the mother wishes to participate in this study.

3.2.10 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with mifepristone. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.2.11 No history of long-term use of corticosteroids or concurrent short term use of corticosteroids is allowed.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Prior to registration, all patients must have given written informed consent for the study. Patients must meet all of the eligibility requirements listed in Section 3. Eligible patients will be entered on study centrally by the University of Chicago study coordinator. All sites should call the study coordinator at (773) 834-1746 or PhaseIICRA@medicine.bsd.uchicago.edu to verify availability of a slot.

Following registration, patients should begin protocol treatment within 7 business days. Issues that would cause treatment delays should be discussed with the Lead Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study will be canceled. The study coordinator/CRA should be notified of cancellations as soon as possible.

4.2 Registration Process

When a potential patient has been identified, notify the University of Chicago Phase II CRA via phone or email to ensure a reservation on the study ((773) 834-1746 or PhaseIICRA@medicine.bsd.uchicago.edu). Reservations for potential subjects will only be held for subjects who have signed consent for that particular study.

When registering a subject, the following must occur:

- Confirm that the institution has a current IRB approval letter for the correct version of protocol/consent and has an annual update on file, if appropriate.
- Submit all required materials (Eligibility Checklist, Source documentation, & signed consent form) to confirm eligibility and required pre-study procedures to the CRA a minimum of 48 hours prior to the subject's scheduled therapy start date.
- Source documentation includes copies of all original documents that support each inclusion/exclusion criteria. The eligibility checklist does not serve as source documentation but rather as a checklist that original source documentation exists for each criterion.
- Communicate with the CRA to ensure all necessary supporting source documents are received and the potential subject is eligible to start treatment on schedule. If there are questions about eligibility, the CRA will discuss it with the PI. PI may clarify, but not overturn, eligibility criteria.
- Affiliate sites must confirm registration of subjects by obtaining a subject study ID number from the CRA via phone, fax or email.
- If a subject does not start on the scheduled day 1 treatment date, promptly inform the CRA as the delay in start may deem the subject ineligible and/or require further or repeat testing to ensure eligibility.
- The date the patient is randomized will be considered the patient's "On Study Date." The patient's subject ID will be assigned and a confirmation of registration will be issued by the CRA on this date. Subjects that sign consent and do not go "OnStudy" will be recorded in the database with the date they signed consent and the reason for not going "OnStudy" (e.g., Ineligible, Screen Failure or Withdrawn Consent).

4.3 Blinding Procedure

For each dose level, patients will be randomized in a 1:1 fashion to receive nab-paclitaxel with mifepristone or placebo. The randomization sequences will be generated by the lead statistician and uploaded into REDCap. The investigational drug pharmacist at each site will then be able to randomize patients who have signed consent to participate in the study. Only the investigational drug pharmacy will be aware of patient's randomization status. Treating physicians, nurses, clinical research assistants, and patients will be blinded to assignment.

4.4 Unblinding Procedure

Patients will be unblinded if they experience a toxicity that the treating investigator feels warrants unblinding. The Treating Investigator will need to contact the Lead Site to obtain permission for unblinding. The Treating Investigator should contact the Lead Site at PhaseIICRA@medicine.bsd.uchicago.edu requesting unblinding and the reason for the unblinding. If unblinding is approved, the treating investigator will contact their IDS pharmacist to obtain the treatment assignment.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Appropriate dose modifications are described in Section 6. Reported adverse events and potential risks are described in Section 8. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

72 patients will be enrolled. All patients will receive nab-paclitaxel 100 mg/m^2 on days 1, 8 and 15 of each 28 day cycle. 36 patients will be randomized to receive placebo and 36 patients will be randomized to receive mifepristone 300 mg daily for one day prior to and the day of each dose of nab-paclitaxel.

PK studies will be performed in the first 20 patients enrolled at pre-specified "PK collecting sites." Patients in this portion of the study will have paclitaxel levels drawn at the following time points: at baseline, and then 15 mins, 45 mins, 4 hrs, 6 hrs, and 24 hrs after completion of nab-paclitaxel infusion. These patients will not receive mifepristone or placebo week one; mifepristone or placebo will start cycle 1, week 2. Paclitaxel levels will be drawn cycle 1/day 1-2 and cycle 1/day 8-9.

Regimen Description					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Nab-Paclitaxel	Patients do not require premedication prior to Nab-Paclitaxel administration, as hypersensitivity reactions are rare.	100 mg/m^2 in 250 ml NS	IV over 30 minutes	Day 1 Day 8 Day 15	28 days (4 weeks)
Mifepristone[x]	Take with food.	300 mg tablet	PO in the a.m. on day prior and day of Nab-Paclitaxel administration	Days 0 and 1 Days 7 and 8 Days 14 and 15	
x – The first 20 patients enrolled at the pre-specified "PK sites" will not receive mifepristone for cycle 1, week 1. Mifepristone or placebo will start with cycle 1, week 2 for these patients.					

The patient will be requested to maintain a medication diary of each dose with the time of self-administration of mifepristone. The medication diary will be returned to clinic staff at the end of each cycle.

5.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of mifepristone with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. Both the Lead Site as well as the site Principal Investigator should be alerted if the patient is taking any agent known to affect (or with the potential to affect) selected CYP450 isoenzymes.

Mifepristone inhibits CYP3A4 and induces CYP3A4. Addition of mifepristone to a pre-existing drug regimen may cause a mild and temporary increase in plasma drug concentration of drugs with significant CYP3A4 metabolism. Medications that are strong inducers of CYP3A4 such as carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentine, St. John's Wort may decrease plasma mifepristone levels. Strong CYP3A4 inhibitor medications are expected to cause the largest increases in plasma mifepristone concentrations. Mifepristone may increase the plasma drug concentration of concomitant medications with metabolism mediated by CYP2C9/2C8. A complete list of drug prohibited on study and those which require close monitoring is provided in Appendix C.

Mifepristone is subject to a significant food effect and therefore must be taken with food.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the Treating Investigator
- Patient refusal
- Lost to follow-up/non-compliance
- Study termination

5.4 Duration of Follow Up

Seventy-two total patients (36 per arm) will be enrolled over 24 months, with a 12 month follow-up period after the last patient has been enrolled.

5.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

General guidelines

- Chemotherapy may be delayed on day 1
- If chemotherapy is skipped on days 8 and/or 15, these doses are not made up. Drug dose reductions are permanent. Once reduced the dose may not be dose escalated
- If chemotherapy dose reduction below dose level -3 is required for toxicity, permanently discontinue study treatment.
- If chemotherapy is delayed or skipped for > 4 weeks for any reason, permanently discontinue study treatment.
- If chemotherapy is held, mifepristone should also be held (although in many instances mifepristone may already have been taken).
- Mifepristone dose will remain at 300 mg. Mifepristone dose may be skipped or permanently discontinued for toxicity, but the dose is not reduced

If mifepristone is skipped for > 4 weeks, permanently discontinue mifepristone. If mifepristone is permanently discontinued or skipped for toxicity, continue chemotherapy unless otherwise specified below

6.1 Nab-paclitaxel dose modifications

Dose Level	Nab-paclitaxel Dose (mg/m2)
0	100
-1	80
-2	60
-3	60 (every other week)

Event	Dose Modification
Neutropenia	
$\geq$ 1,000/mm^3	No dose modification is required.
<1000/mm^3	1st occurrence: Delay until ANC $\geq$ 1000 and reduce dose permanently by 1 level with next dose. 2nd occurrence: Delay until ANC $\geq$ 1000 and reduce dose permanently by 1 level with next dose. 3rd occurrence: Delay until ANC $\geq$ 1000. Reduce frequency to every other week dosing with next dose and initiate G-CSF.

	If patient continues to have neutropenia despite institution of G-CSF and 3 dose modifications, protocol therapy should be discontinued permanently
Thrombocytopenia	
$\geq$ 100,000/mm^3	No dose modification is required
75,000-99,999/mm^3	1st occurrence: No dose modification is required. Subsequent occurrence: Chemotherapy should be reduced by one dose level (maximum of 3 dose reductions allowed) for all subsequent doses
< 75,000	Delay dose until platelets $\geq$ 75,000/ mm^3. Decrease dose by one level for all subsequent doses (maximum of 3 dose reductions allowed)
Hypersensitivity Reaction	
Grade 1	No dose modification required
Grade 2	No dose modification required. Add Benadryl and H2 blocker with subsequent cycles.
Grade 3	Permanently discontinue chemotherapy.
Grade 4	Permanently discontinue chemotherapy.
Hepatotoxicity	
Grade 1	No dose modification is required.
Grade 2	Decrease dose by one dose level.
Grade 3	Hold until improves to grade 1. Decrease by one dose level for all subsequent doses.
Grade 4	Discontinue chemotherapy permanently.
Hepatotoxicity	
Grade 1	No dose modification is required.
Grade 2	Decrease dose by one dose level.
Grade 3	Hold until improves to grade 1. Decrease by one dose level for all subsequent doses.
Grade 4	Discontinue chemotherapy permanently.
Peripheral Neuropathy	
Grade 1	No dose modification is required.
Grade 2	Hold until neuropathy improves to grade 1. Decrease dose level by one (maximum of two dose reductions allowed).
Grade 3	Hold until neuropathy improves to grade 1. Decrease dose level by one (maximum of two dose reductions allowed).
Grade 4	Hold until neuropathy improves to grade 2. Decrease dose level by one (maximum of two dose reductions allowed).
Other clinically significant toxicities excluding fatigue, alopecia, hypokalemia, and leukopenia	
Grade 1	No dose modification is required.
Grade 2	No dose modification is required.

Grade 3	Hold until toxicity improves to grade 1. Decrease dose level by one for all subsequent doses.
Grade 4	Discontinue study treatment permanently.

6.2 Mifepristone Dose modification

- Mifepristone dose will remain at 300 mg. Mifepristone dose may be skipped or permanently discontinued for toxicity, but the mifepristone dose is not reduced.

- If mifepristone is skipped for > 3 weeks, permanently discontinue mifepristone.

- If patient experiences grade 3 or 4 rash thought to be related to mifepristone, then mifepristone will be discontinued permanently.

- If mifepristone is permanently discontinued or skipped for toxicity, continue chemotherapy unless otherwise specified as described above.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. A list of AEs expected by the investigational agent(s) can be found in Section 8.

7.1 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 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **Attribution** of the AE:
  - Definite (5) – The AE *is clearly related* to the study treatment.
  - Probable (4) – The AE *is likely related* to the study treatment.
  - Possible (3) – The AE *may be related* to the study treatment.
  - Unlikely (2) – The AE *is doubtfully related* to the study treatment.
  - Unrelated (1) – The AE *is clearly NOT related* to the study treatment.

7.2 Adverse Event Definitions

7.2.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including a laboratory finding), symptom or disease temporally

associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

At each evaluation patients should be interviewed in a non-directed manner to elicit potential adverse reactions from the patient. The occurrence of an adverse event will be based on changes in the patient's physical examination, laboratory results, and/or signs and symptoms, and review of the patient's own record of adverse events.

Adverse events will be followed until resolution while the patient remains on-study. Once the patient is removed from study, events thought to be related to the study medication will be followed until resolution or stabilization of the adverse event, or until the patient starts a new treatment regimen, or death, whichever comes first. Subjects will be followed for AEs/SAEs from the time the informed consent is signed to 30 days after their last dose of study drug(s).

7.2.2 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study related therapy, or within (6 months from the subject's last dose of study related therapy), are considered immediately reportable events. Study related therapy is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Lead Site immediately at PhaseIICRA@medicine.bsd.uchicago.edu, The female subject should be referred to an appropriate healthcare professional for further evaluation.

The Treating Investigator will follow the female subject until completion of the pregnancy, and must notify the Lead Site at PhaseIICRA@medicine.bsd.uchicago.edu about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Treating Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to the Lead Site at PhaseIICRA@medicine.bsd.uchicago.edu, within 24 hours of the Treating Investigator's knowledge of the event.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Treating Investigator suspects is related to the in utero exposure to the study related therapy should also be reported to the Lead Site at PhaseIICRA@medicine.bsd.uchicago.edu, within 24 hours of the Treating Investigator's knowledge of the event.

Male Subjects: If a female partner of a male subject taking study based therapy becomes pregnant, the male subject taking study related therapy should notify the Treating Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. Male patients treated with nab-paclitaxel are advised not to father a child during and up to 6 months after treatment.

7.2.3 Overdose

Overdose, as defined for this protocol, refers to nab-paclitaxel dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of nab-paclitaxel assigned to a given patient, regardless of any associated adverse events or sequelae.

PO	any amount over the protocol-specified dose
IV	10% over the protocol-specified dose
SC	10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported to the Lead Site at PhaseIICRA@medicine.bsd.uchicago.edu.

7.2.4 Serious Adverse Events

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) Life-threatening (e.g. places subject at immediate risk of death, this does not include events that might have caused death if they occurred a greater severity)
3) Results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) An Important Medical Event

Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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.

7.2.5 Unexpected Events

Unexpected events are those not listed at the observed specificity or severity in the protocol, informed consent, or FDA-approved package insert. An event is considered unexpected if it is listed as occurring within the class of drugs or otherwise expected from the drug's pharmacological properties but which has not been previously observed with this specific investigational agent.

7.2.6 Adverse Reactions

An adverse event is considered to be an adverse reaction if there evidence to suggest a causal relationship to the study agent. This may include a single occurrence of an event strongly associated with drug exposure (e.g. Stevens-Johnson Syndrome), one or more occurrence of an event otherwise uncommon is the study population, or an aggregate analysis of specific events occurring at greater than expected frequency.

7.2.7 Adverse Events of Special Interest (AESIs)

AESIs are defined as any of the following events, irrespective of the level of severity:

- endometrial hyperplasia and/or vaginal bleeding
- retinopathy
- major adverse cardiovascular events (MACE) which include death related to coronary or cerebrovascular disease, acute myocardial infarction, stroke, and revascularization (coronary or cerebral)

7.3 Adverse Event Reporting Requirements

7.3.1 Routine Serious Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. S**AEs reported using the Serious Event Reporting Form and/or MedWatch Form discussed below must <u>also</u> be reported in routine study data submissions.**

All adverse events (except grade 1 and 2 laboratory abnormalities that do not require an intervention), regardless of causal relationship, are to be recorded in the case report form and source documentation. The Treating Investigator must determine the intensity of any adverse events according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 and their causal relationship.

7.3.2 Serious Adverse Event Reporting **<u>to</u>** the Coordinating Center

Use the UC CCC protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

All serious adverse events and all adverse events of special interest (AESIs) [as defined in sections 7.2.4 and 7.2.7] occurring on this study require reporting to the University of Chicago Comprehensive Cancer Center (UCCCC). The responsible Research Nurse or other designated individual at the treating site should report the SAE/AESI to the Study Lead Investigator, the University of Chicago CRA and the CCTO by the end of the business day when s/he becomes aware of the event. Events occurring after business hours should be reported to the CCTO by 12pm (noon) the next business day. Please scan and send via email (preferred) or fax to the following:

University of Chicago Phase II CRA:
PhaseIICRA@medicine.bsd.uchicago.edu
Phone: 773-834-1746
Fax: 773-702-4889

UC CCC Cancer Clinical Trials Office Quality Assurance:
qaccto@bsd.uchicago.edu

All unexpected adverse reactions must be reported to the IND holder so that the University of Chicago CCTO can inform the FDA. The responsible Research Nurse or other designated individual at the treating site should provide a complete written report using the FDA MedWatch 3500A form. The completed form should be sent to the CCTO at qaccto@bsd.uchicago.edu and to the Phase II CRA at PhaseIICRA@medicine.bsd.uchicago.edu within the specified timelines above regardless of whether all information regarding the event is available. If applicable, a follow-up report should be provided to the CCTO if additional information on the event becomes available.

Participating sites should not forward any adverse event reports directly to the FDA. The CCTO will report all events to the FDA as per the current FDA guidelines.

All serious adverse events should also be reported to the local IRB of record according to their policies and procedures.

7.3.3 Serious and Unexpected Adverse Event reporting **by** the Coordinating Center

The designated UC CCC Regulatory Manager will notify all participating sites of all unexpected and serious adverse reactions that occur on this clinical trial and which are reported to the FDA and/or UC Institutional Review Board (IRB).
All serious and/or unexpected adverse drug experiences, and all adverse events of special interest (AESIs) that occur during the course of the study shall be reported to Corcept by the Lead Site. The Lead Site will notify Corcept each time that a "follow up" report is made to the IRB.
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8. PHARMACEUTICAL INFORMATION

8.1 Investigational Agent Description and Management: Mifepristone

8.1.1 **Product description**: Mifepristone and placebo tablets will be provided by Corcept Therapeutics in 300 mg tablets.

8.1.2 **Storage requirements:** Store at controlled room temperature, 25°C; excursions permitted to 15 to 30°C. When stored under these conditions, the shelf-life of mifepristone is at least 30 months.

8.1.3 **Route of administration:** Oral

8.1.4 **Adverse effects**:

Central nervous system: headache, dizziness, fatigue, insomnia, anxiety

Cardiovascular: syncope

Dermatologic: rash

Gastrointestinal: abdominal pain, nausea, vomiting, diarrhea, dyspepsia

Genitourinary: uterine cramping, uterine hemorrhage, vaginitis, pelvic pain

Hematologic: anemia, neutropenia, leukopenia

Neuromuscular: back pain, rigors, leg pain, weakness

Respiratory: dyspnea

Other: hypokalemia, sinusitis, nasopharyngitis

8.2 Commercial Agent: Nab-paclitaxel (Abraxane)

8.2.1 Product description: Nab-paclitaxel is commercially available in single-dose vials. Each single-use 50 mL vial contains paclitaxel (100mg) and approximately 900 mg of human albumin as a stabilizer. Each vial is supplied as a white to off-white sterile lyophilized powder.

8.2.2 Solution preparation: Each vials of nab-paclitaxel lyophilized powder is reconstituted in 20 mL of 0.9 NS.

8.2.3 Storage requirements**:** Un-reconstituted nab-paclitaxel should be stored at 20-25^{o}C in its carton. Reconstituted nab-paclitaxel should be used immediately. If not used immediately, the vial must be place in its carton and stored at 2-8 ^{o}C for a maximum of 8 hours. Both forms should be stored in an area free of environmental extremes and must be accessible only to study personnel.

8.2.4 Route of administration**:** Nab-paclitaxel is injected into a vein [intravenous (I.V.) infusion] over 30 minutes. Following administration, the intravenous line should be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure complete administration of the complete dose, according to local practice.

8.2.5 Adverse effects

Cardiovascular: ECG abnormalities, edema, hypotension, chest pain, cardiac arrest, supraventricular tachycardia, thrombosis, thromboembolism

Dermatologic: alopecia

Gastrointestinal: nausea, diarrhea, vomiting, mucositis

Hematologic: neutropenia, anemia, myelosuppression, bleeding, neutropenic fever

Hepatic: increase in liver function tests

Neuromuscular: sensory neuropathy, weakness, myalgias, arthralgias

Ocular: visual disturbance

Renal: elevation in creatinine

Respiratory: dyspnea, cough

Other: infection, hypersensitivity reaction

8.2.6 Drug distribution

Mifepristone ordering information will be provided in the laboratory manual.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Glucocorticoid Receptor (GR) expression in tumor tissue

Patients must have tumor block or slides available for testing, and tumor must be glucocorticoid receptor positive (defined as GR > 10% moderate to strongly positive by central lab) as determined by central CLIA lab.

Fifteen (15) unstained sections of primary tumor or metastatic tumor or both will be requested for each patient enrolled on study. Sections should be 3-5 microns in thickness and mounted on positively charged slides. Fine needle aspirates or other alternative cytology samples are not acceptable. Slides should be sent accompanied by the tumor sample submission form and the de-identified original pathology report as per the laboratory manual and sent to:

QualTek Clinical Laboratories
6483 Calle Real, Suite A
Goleta, CA 93117

9.2 Pharmacokinetic Studies

To expand and follow up on our understanding of a potential PK interaction between nab-paclitaxel and mifepristone, we will perform PK studies in the first 20 patients enrolled at pre-specified "PK sites".

Patients in this portion of the study will have paclitaxel levels drawn at pre-specified time points (at baseline, and then 15 mins, 45 mins, 4 hrs, 6 hrs, and 24 hrs after completion of nab-paclitaxel administration). These patients will not receive mifepristone or placebo during cycle one week one; mifepristone or placebo will start cycle one week two. Paclitaxel levels will be drawn cycle 1/day 1-2 and cycle 1/day 8-9.

For paclitaxel levels being collected at the University of Chicago: blood will be drawn in 10 ml heparin vacutainers (green tops) to be spun down immediately after collection at 3000xg for 15 minutes in a refrigerated centrifuge at 4°C. Plasma will then be transferred to two cryovials and stored at -80°C. Plasma samples will be labeled with patient's initials and ID number, protocol number, initials of phlebotomist, and sample ID (i.e. D1 baseline, D2 24 hrs, etc). Actual blood sampling times will be noted for each patient on the pharmacokinetic sample collection form. Any delay or problems will be carefully noted under comments along with the initials of the phlebotomist.

Samples drawn at UC will be stored in the BioFluids Core Facility (AB201 & AB204, Billings) prior to transfer on dry ice to the Pharmacology Core (KCBD 7160).

For paclitaxel levels collected at a site other than University of Chicago: blood will be drawn in 10 ml heparin vacutainers (greentops) to be spun down immediately after collection at 3000xg for 15 minutes in a refrigerated centrifuge at 4°C. Plasma will then be transferred to two cryovials and stored at -80°C. Samples will be labeled with patient's initials and ID number, protocol number, initials of phlebotomist, and sample ID (i.e. D1 baseline, D2 24 hrs, etc). Actual blood sampling times will be noted for each patient on the sample collection form. Any delay or problems will be carefully noted under comments along with the initials of the phlebotomist. Samples from the same patient will be batched and shipped together, accompanied by completed pharmacokinetic sample collection forms for each sample.

Patient samples should be shipped frozen on dry ice accompanied by the PK sample submission form by an overnight delivery service as per the laboratory manual.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Scans and x-rays must be done $\leq$ 4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	Cycle 1						Cycle 2 and beyond[f]	Off Study[b]
		Day 0	Day 1	Day 7	Day 8	Day 14	Day 15		
Mifepristone[a]		X	X	X	X	X	X		
Nab-paclitaxel			X		X		X		
Informed consent	X								
Demographics	X								
Medical history	X								
Concurrent meds	X	X ----------X							
Physical exam	X		X						X
Vital signs	X		X		X		X		X
Height	X								
Weight	X		X		X		X		X
Performance status	X		X						X
CBC w/diff, plts	X		X		X		X		X
Serum chemistry[c]	X		X		X		X		X
Adverse event evaluation		X ----------X							X
Tumor measurements	X	Tumor measurements are repeated every 8 weeks (2 cycles). Documentation (radiologic) must be provided for patients removed from study for progressive disease[e].							X[b]
Radiologic evaluation	X	Radiologic measurements should be performed every 8 weeks (2 cycles).							X[b]
B-HCG	X[d]								
TSH	X								
Serum cortisol	X								
Tissue collection	X								

a: First 20 patients enrolled at pre-specified "PK sites" will not receive mifepristone or placebo for cycle 1, week 1. They will start study drug or placebo for cycle 1, week 2.
b: Off-study evaluation.
c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
d: Serum pregnancy test (women of childbearing potential).
e: After 4 cycles of therapy, imaging can be spaced out to every 3rd cycle if treating physician feels it is clinically appropriate.
f: After cycle 1 of therapy, the treating physician does have flexibility for scheduling treatment days (ie, a two day window for the weekly treatment or omission of a week if needed).

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks (2 cycles).

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) [*Eur J Ca* 45:228-247, 2009]. 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.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with mifepristone.

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

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

11.1.2 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 or as ≥10 mm with CT scan, MRI, or 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 will be considered measurable provided they have increased in size following the completion of radiation, and that radiation was completed at least 4 weeks in advance of initiating protocol therapy.

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.

11.1.3 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.

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.

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.

11.1.4 Response Criteria

11.1.4.1 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.

11.1.4.2 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 Lead Principal Investigator).

11.1.4.3 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.

11.1.5 Confirmatory Measurement/Duration of Response

Confirmation
To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed between 6-8 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks).

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.

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from date of randomization to time of progression or death, whichever occurs first.

12. DATA REPORTING

Data reporting will be performed utilizing the eVelos electronic data capture system. The University of Chicago CRA will provide you with the applicable user registration information.

All required data must be recorded in the eVelos database at the completion of each cycle. AEs are to be entered in real time. SAEs are to be entered on the Serious Event Form within 24 hours of the site's knowledge of the event and sent via email (preferred) or fax to the University of Chicago (PhaseIICRA@medicine.bsd.uchicago.edu or qaccto@bsd.uchicago.edu; Fax: 773-702-4889). All case report forms must be completed by designated study personnel. Each screened (consented) patient is to be entered into eVelos within 48 hours of patient registration. In addition to direct data entry, you may be required to provide supporting source documentation. Source records are original documents, data, and records (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. Each site will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the case report form.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a randomized, double-blind, placebo-controlled phase II trial comparing nab-paclitaxel plus mifepristone versus nab-paclitaxel plus placebo using progression-free survival (PFS)as the primary endpoint.

13.2 Sample Size/Accrual Rate

Seventy-two total patients (36 per arm) will be enrolled over 12 months, with a 12 month follow-up period after the last patient has been enrolled. Assuming 90% of patients are GR+, this is expected to yield 64 GR+ patients (32 per arm). The primary objective is to compare progression-free survival (PFS) between the two treatment arms in the GR+ subgroup. Internal Celgene data reveals that patients with TNBC who received single agent nab-paclitaxel as second-line or greater therapy have a PFS of 3.15 months.

The sample size is determined based on the Phase II screening design proposed by Rubinstein et al (JCO, 2005). Assuming the monotherapy arm has median PFS of 3.15 months, a sample size of 64 GR+ patients (n=32 per arm) will achieve 80% power to detect a hazard ratio HR =0.61 using a one-sided logrank test with alpha=15% significance level. This calculation assumes 5% annual loss to follow-up rate. Hazard ratio HR=0.61 corresponds to the median PFS of 5.18 months in the combination arm, and the expected number of events in the two arms is 31 and 28, respectively. Descriptive analyses will be conducted in the small number of anticipated GR- patients.

13.3 Stratification Factors

Randomization will be stratified according to the number of prior cytotoxic therapies received (0 vs. 1-2) using the method of permuted blocks. When the next patient is to be randomized, the UC research coordinator will email the IDS pharmacist at the site where the patient is being enrolled and provide the pharmacist with the patient ID number, patient initials, and stratum (0 vs.1-2 prior therapies). The IDS pharmacist will log in to REDCap to obtain the treatment assignment.

13.4 Analysis of Secondary Endpoints

We will perform PK analysis on the first 20 patients who are enrolled at a PK collection site as discussed prior.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment.

13.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions should be based on all eligible patients. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

14. STUDY MANAGEMENT AND REGULATORY AFFAIRS

14.1 Multicenter Guidelines

The specific responsibilities of the Lead Principal Investigator and the Coordinating Center are presented in Appendix B. Clinical studies coordinated by The University of Chicago must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements

The Study Lead PI/Coordinating Center is responsible for distributing all official protocols, amendments, and IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

14.2 Institutional Review Board (IRB) Approval and Consent

Unless otherwise specified, each participating institution must obtain its own IRB approval. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

14.3 Food and Drug Administration (FDA) Approval

This study will be conducted under an IND held by Dr. Rita Nanda at the University of Chicago. The University of Chicago CCTO will be responsible for facilitating all communications with the FDA on behalf of the IND holder. Participating sites should not communicate directly with the FDA.

14.4 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Cancer Clinical Trials Office (CCTO) at the University of Chicago Comprehensive Cancer Center.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the Site Principal Investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Investigational drug accountability standard operating procedures
- Additionally, before the study can be initiated at any site, the required executed research contract/subcontract must be on file with the University of Chicago.

14.5 Data and Safety Monitoring

This study will be remotely monitored by the designated University of Chicago Clinical Research Associate (CRA) in accordance with the University of Chicago, Section of Hematology/Oncology standard operating procedure titled Monitoring of Multi-Institutional Investigator Initiated Clinical Trials.

Prior to subject recruitment, and unless otherwise specified, a participating site will undergo a Site Initiation Teleconference to be conducted by the designated University of Chicago research team. The site's principal investigator and his or her study staff must attend the site initiation meeting.

Monitoring will be conducted to verify the following:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Compliance with regulations
- Submission of required source documents

Participating sites will also undergo a site close-out teleconference upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and to ensure that the Site Investigator is aware of his/her ongoing responsibilities.

Unless otherwise specified, this protocol will undergo weekly review at the multi-institutional data and safety monitoring teleconference as per procedures specified by the UC CCC NCI-approved Data and Safety Monitoring Plan. The conference will review:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Protocol deviations are to be documented using the Protocol Deviation Form and sent via email to PhaseIICRA@medicine.bsd.uchicago.edu. Deviations that are considered major because they impact subject safety or alter the risk/benefit ratio, compromise the integrity of the study data, and/or affect subjects' willingness to participate in the study must be reported

within 7 days. Please contact the University of Chicago CRA (PhaseIICRA@medicine.bsd.uchicago.edu) if you have questions about how to report deviations. All major protocol deviations should also be reported to the local IRB of record according to their policies and procedures.

14.6 Auditing

In addition to the clinical monitoring procedures, the University of Chicago Comprehensive Cancer Center will perform routine Quality Assurance Audits of investigator-initiated clinical trials as described in the NCI-approved UC CCC DSM Plan. Audits provide assurance that trials are conducted and study data are collected, documented and reported in compliance with the protocol. Further, quality assurance audits ensure that study data are collected, documented and reported in compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements. The audit will review subjects enrolled at the University of Chicago in accordance with audit procedures specified in the UC CCC Data and Safety Monitoring plan. For institutions who are formal members of the Personalized Cancer Care Consortium (PCCC), the UC CCC will conduct on site quality assurance audits on average every two years during the enrollment and treatment phase of the study.

Auditing procedures for participating sites that are not full members of the PCCC must be specified and approved by the UC CCC Clinical Research Advisory Committee. In general, for sites that are not full members of the PCCC, auditing responsibility will be delegated to the participating center, with the annual audit report forwarded to the University of Chicago for review.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the University of Chicago Cancer Clinical Trials Office and Regulatory Manager that such a request has been made.

14.7 Amendments to the Protocol

All modifications to the protocol, consent form, and/or questionnaires will be submitted to the University of Chicago IRB for review and approval. A list of the proposed modifications or amendments to the protocol and/or an explanation of the need of these modifications will be submitted, along with a revised protocol incorporating the modifications. Only the Study Lead PI can authorize any modifications, amendments, or termination of the protocol. Once a protocol amendment has been approved by the University of Chicago IRB, the Regulatory Manager will send the amended protocol and consent form (if applicable) to the affiliate institutions electronically. Upon receipt of the packet the affiliate institution is expected to do the following:

- The affiliate must reply to the email from the Regulatory Manager indicating that the amendment was received by the institution and that it will be submitted to the local IRB.

- The amendment should be submitted to the affiliate institution's IRB as soon as possible after receipt. The amendment **must** be IRB approved by the institution

within 3 months from the date that it was received.

- **The University of Chicago version date and/or amendment number must appear on the affiliate consent form and on the affiliate IRB approval letter.** The version dates can be found on the footer of every page of the protocol and consent form. The amendment number can be found on the University of Chicago IRB amendment approval letter that is sent with the protocol/amendment mailing.

- The IRB approval for the amendment and the amended consent form (if amended consent is necessary) for the affiliate institution must be sent to the designated UC Regulatory Manager as soon as it is received.

14.8 Annual IRB Renewals, Continuing Review and Final Reports

A continuing review of the protocol will be completed by the University of Chicago IRB and the participating institutions' IRBs at least once a year for the duration of the study. The annual IRB renewal approvals for participating institutions should be forwarded promptly to the Regulatory Manager. If the institution's IRB requires a new version of the consent form with the annual renewal, the consent form should be included with the renewal letter.

14.9 Record Retention

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

14.10 Obligations of Study Site Investigators

The Study Site Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Study Site Principal Investigator is responsible for personally overseeing the treatment of all study patients. He/she must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Study Site Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the CRFs. Periodically, monitoring visits or audits will be conducted and he/she must provide access to original records to permit verification of proper entry of data.

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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

MULTICENTER GUIDELINES

Responsibility of the Study Lead PI

- The Study Lead PI will be the single liaison with regulatory and data management staff, outside sponsor/s, FDA, and funding agencies The Study Lead PI is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Study Lead PI. There will be only one version of the protocol, and each participating institution will use that document. The Study Lead PI is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Study Lead PI is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements are the responsibility of the Study Lead PI.
- The Study Lead PI is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Study Lead PI will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- The Coordinating Center is responsible for maintaining copies of IRB approvals from each participating site.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Study Lead PI.
- The Coordinating Center will maintain documentation of AE reports. The Coordinating Center will submit AE reports to the Study Lead PI for timely review.

APPENDIX C

CONCOMITANT MEDICATION RESTRICTIONS

CYP3A4 Substrate medications

Mifepristone inhibits CYP3A4 and induces CYP3A4. The induction of CYP3A4 becomes maximal after 7-10 days of dosing. Addition of mifepristone to a pre-existing drug regimen may cause a moderate and temporary increase in plasma drug concentration of drugs with significant CYP3A4 metabolism. Induction of CYP3A4 by mifepristone is expected to reduce plasma concentrations of CYP3A4 substrates after several doses of mifepristone. When a concomitant CYP3A4 substrate medication is added onto chronic mifepristone dosing, there may be a decrease in plasma drug concentrations of the CYP3A4 substrate. Concomitant medications that are subject to the greatest decreases in plasma drug concentration are those orally administered drugs with a large first pass metabolism mediated largely or solely by CYP3A4. In addition, mifepristone is a substrate for CYP3A4 and strong inhibitors of CYP3A4 are expected to increase exposure to mifepristone.

The following drugs have these characteristics and are not allowed during the study:

- cyclosporine, tacrolimus, sirolimus
- HIV protease inhibitors including amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir, ritonavir, tipranavir, darunavir, boceprevir
- non-nucleoside reverse transcriptase inhibitors including delavirdine, nevirapine, efavirenz, etravirine
- kinase inhibitors including erlotinib, imatinib, sunitinib, nilotinib, dasatinib
- dihydroergotamine, ergotamine
- fentanyl
- pimozide
- conivaptan
- itraconazole, voriconazole, posaconazole
- clarithromycin, telithromycin
- certain HMG CoA reductase inhibitors (statins): lovastatin, simvastatin, atorvastatin
- certain benzodiazepines: (midazolam [orally administered], triazolam, alprazolam)
- Other CYP3A4 substrates although not absolutely prohibited during the study may require careful monitoring and/or dose adjustment. These include the following drugs or drug classes:
- Calcium Channel Blockers except amlodipine
- Phosphodiesterase Type 5 inhibitors (sildenafil, vardenafil, tadalafil)
- Benzodiazepines (diazepam, clonazepam, chlordiazepoxide, brotizolam, estazolam, flunitrazepam, flurazepam, lormetazepam, nimetazepam, nitrazepam, temezepam, bromazepam, chlorazepate, prazepam) but not lorazepam or oxazepam
- Benzodiazepine related hypnotics (zolpidem, zaleplon, eszopiclone)
- Anti-arrhythmic drugs including amiodarone, quinidine, encainide

Several options are available for managing increases in the levels of concomitant medications that are 3A4 substrates during mifepristone therapy:

Management during the initial inhibitory phase

CYP3A4 inhibition occurs and will predominate starting with the first dose of mifepristone and will last for 3 to 4 days. During this time, the acute effects of raised plasma concentrations of the concomitant medication may be monitored clinically for lack of tolerability by keeping subjects under direct observation for several hours after the first dose of mifepristone and the concomitant medication. If the concomitmant medication is not tolerated, then therapy should be discontinued, or the dose lowered to the minimal dose. Alternatively, the concomitant medication may be stopped for several days and reintroduced after the acute CYP3A4 inhibitory phase has passed. After restarting the concomitant medication, subjects should be followed for loss of efficacy and a potential need for increasing dose of the concomitant medication.

Management of mifepristone withdrawal after 7-day mifepristone administration

Because CYP3A4 induction will decrease exponentially over a period of several weeks after stopping mifepristone, any change in dose of a concomitant medication during mifepristone therapy will need to be re-evaluated. Caution should be used when introducing new drugs in the first weeks after discontinuing mifepristone due to residual effects of CYP3A4 induction.

CYP3A4 inducer medications

Medications that are strong inducers of CYP3A4 such as carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentine, St. John's Wort may decrease plasma mifepristone levels. Somewhat higher mifepristone doses may be required in subjects taking these concomitant medications. Mifepristone should not be used in doses higher than those defined in the protocol.

CYP3A4 inhibitor medications

Strong CYP3A4 inhibitor medications are expected to cause the largest increases in plasma mifepristone concentrations. The following strong CYP3A4 inhibitor medications are not allowed during the study:

- ketoconazole, itraconazole, voriconazole, posaconazole
- nefazodone
- ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir
- saquinavir, telaprevir
- clarithromycin, telithromycin
- conivaptan

Contraindicated medications must be discontinued and cleared from a patients system prior to baseline (Study Day 0). The timing of medication discontinuation is based on the specific half-life of the parent compound and its active metabolites. Hence, contraindicated medications must be discontinued 7 days or 5 half-lives, whichever is greater, prior to baseline (Study Day 0).

CYP2C9/2C8 substrate medications

Mifepristone may increase the plasma drug concentration of concomitant medications with metabolism mediated by CYP2C9/2C8. Drugs with the largest increases will be those whose metabolism are largely or solely mediated by CYP2C9/2C8 and include:

- Non-steroidal Anti-inflammatory drugs (NSAIDs)
- Warfarin

NSAIDs should be used at lower doses. For patients receiving warfarin, lower doses should be used during introduction of mifepristone; the prothrombin time should be carefully monitored to avoid over anticoagulation. The prothrombin time should be measured after the first dose of mifepristone and frequently thereafter. Prolongation of prothrombin time may not appear for a week or longer after mifepristone treatment begins. Any change in dose of a concomitant medication during mifepristone therapy will need to be re-evaluated after cessation of mifepristone.

P-glycoprotein substrates

Effects of mifepristone on p-glycoprotein are expected to be modest due to both inhibition and delayed induction. Effects of potential clinical significance are expected only for drugs with a narrow therapeutic margin of which digoxin is the main concern. Lower doses of digoxin should be considered when starting mifepristone. Adjustments to digoxin should be made during mifepristone and should be guided by blood digoxin levels.

Corticosteroids

All systemic corticosteroids are prohibited. Mifepristone is contraindicated in patients who require concomitant treatment with systemic corticosteroids for serious medical conditions or illnesses (e.g., immunosuppression after organ transplantation) because mifepristone antagonizes the effect of glucocorticoids.

- Adrenostatic medications
- Adrenostatic medications includingmetyrapone, ketoconazole, fluconazole, aminoglutethimide, etomidate are prohibited.
- Neuromodulator drugs
- Neuromodulator drugs that act at the hypothalamic-pituitary level, such as serotonin antagonists (cyproheptadine, ketanserin, retanserin) dopamine agonists (bromocriptine, cabergoline), GABA agonists (sodium valproate), and somatostatin receptor ligands (octreotide) are prohibited.