BRE 203

A Phase II Study with Orteronel as Monotherapy in Patients with Metastatic Breast Cancer (MBC) that Expresses the Androgen Receptor (AR)

SCRI DEVELOPMENT INNOVATIONS STUDY NUMBER:	BRE 203
STUDY DRUG:	Orteronel
SPONSOR:	SCRI Development Innovations, LLC (SCRI Innovations) 3322 West End Avenue, Suite 900 Nashville, TN 37203 1-877-MY-1-SCRI
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DATE FINAL:	01 October 2013 Version 2.0

AMENDMENT NUMBER:	1	**AMENDMENT DATE:**	30 October 2013

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BRE 203 Clinical Study Protocol Statement of Compliance

This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act**

As the Study Chair, I understand that my signature on the protocol constitutes my agreement and understanding of PI responsibilities to conduct the research trial in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

Clinical Study Protocol Approval Page

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Howard A. Burris, III, MD,		
Study Chair	**Study Chair Signature**	**Date**
Sheetal Khedkar		
SCRI Development Innovations, LLC Representative	**SCRI Development Innovations, LLC Representative Signature**	**Date**

Clinical Study Principal Investigator Signature Form

A Phase II Study with Orteronel as Monotherapy in Patients with Metastatic Breast Cancer (MBC) that Expresses the Androgen Receptor (AR)

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DATE FINAL:		01 October 2013	
AMENDMENT NUMBER:	**1**	**AMENDMENT DATE**:	30 October 2013

By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

_____	_____	_____
Principal Investigator Name (Please Print)	**Principal Investigator Signature**	**Date**

Please retain a copy of this page for your study files and return the original signed and dated form to:

SCRI Development Innovations, LLC
3322 West End Avenue, Suite 900
Attn: BRE 203 Study Team
Nashville, TN 37203

BRE 203 Summary of Change

AMENDMENT NUMBER: 1 **AMENDMENT DATE:** 30 October 2013

Global Changes

Patients who experience Grade 4 non-hematologic toxicity will permanently discontinue study drug.

Section 3.1 Inclusion Criteria

4) In addition to having AR+ tumors, patients must fit into 1 of the 2 following categories:

- Triple negative (ER-/PR-/HER2-) (*Note: This group of patients must have received at least 1 and up to 3 prior chemotherapy regimens* ***in the advanced setting***.)
- ER+ and/or PR+ (*Note: This group of patients must have received at least 1 and up to 3 prior hormonal therapies and at least one prior chemotherapy treatment in the advanced setting. HER2+ patients in this group must have received* ***a minimum of 2 lines of HER2-directed therapy in the advanced setting*** ~~*at least 1 trastuzumab-containing regimen for metastatic disease*~~.) This group of patients may be pre-menopausal with ovarian suppression or post-menopausal. LHRH agonists maybe used to render ovarian suppression with post-menopausal ranges of estradiol or FSH per institutional guidelines.

Section 3.2 Exclusion Criteria

19) ***Use of a prohibited concomitant medication (see Section 5.3.2 and Appendix D) that cannot be safely discontinued or substituted.***

Section 5.3.2 Prohibited Concomitant Medications

- Concomitant treatment with any medication that may cause QT prolongation or Torsade*s* de Pointes (see Appendix D). If a patient, after study enrollment, requires use of a medication that may cause QT prolongation and/or Torsades de Pointes ***that cannot be safely substituted***, the patient must be removed from the study.

BRE 203 CLINICAL PROTOCOL SYNOPSIS

Title of Study:	A Phase II Study with Orteronel as Monotherapy in Patients with Metastatic Breast Cancer (MBC) that Expresses the Androgen Receptor (AR)	
SCRI Innovations Protocol Number:	BRE 203	
Sponsor:	SCRI Development Innovations, LLC	
Study Duration:	The total duration of the study is planned to be 48 months (enrollment and active treatment).	**Phase of Study:** II
Study Centers:	This is a multicenter study to be conducted in the United States at approximately 15 sites.	
Patient Population	This study will enroll patients with MBC who have progressed on prior hormonal/ chemotherapy regimens and whose cancer expresses AR. Patients will be enrolled onto one of the 2 following cohorts based on their tumor specificity: • Cohort 1: Patients with estrogen receptor negative (ER-)/progesterone receptor negative (PR-)/ human epidermal growth factor receptor 2 negative (HER2-)/AR positive (+) MBC with 1 to 3 previous treatments for metastatic disease • Cohort 2: Postmenopausal women with ER+ and/or PR+/AR+ refractory MBC who have progressed after at least one, and up to 3, previous hormonal treatments for metastatic disease.	
Objectives:	**Primary Objectives** The primary objectives of this study are to evaluate: • Response rate (RR) and disease control rate (DCR) following treatment with orteronel in patients with refractory metastatic triple-negative breast cancer expressing AR (ER-/PR-/HER2-/AR+) • Response rate and disease control rate (DCR) following treatment with orteronel in patients with refractory ER+ and/or PR+/AR+ breast cancer. **Secondary Objectives** The secondary objectives of this study are to evaluate: • Safety and tolerability of the regimen • Measurement of changes in serum estradiol levels, total and free testosterone levels, and sex hormone binding globulin (SHBG) during treatment with orteronel • Measurement of changes in adrenocorticotropic hormone (ACTH), dehydroepiandrosterone sulfate (DHEA-S), and cortisol levels during treatment with orteronel • Progression-free survival (PFS) • Overall survival (OS). **Exploratory Objective** As an exploratory objective of this trial: • Archived tumor tissue will be assayed for the following biomarkers: loss of phosphatase and tensin homolog (PTEN) and phosphatidylinositol 3-kinase (PIK3CA) mutation.	
Number of Patients:	Up to 86 patients are planned to be enrolled in this study (6 for the lead-in phase and 80 for continuous study treatment).	
Study Design:	This is an open-label multicenter study to be conducted in 2 stages. All patients will receive orteronel orally (PO) at a dose of 300 mg twice daily (BID). • Lead-in Phase: The first 6 patients treated will be evaluated to confirm the safety and feasibility of this regimen. After all 6 patients complete at least 4 weeks of treatment, and if no prohibitive toxicities are identified, continuous study treatment will begin.	

BRE 203 CLINICAL PROTOCOL SYNOPSIS

Study Design (continued):	• Continuous Study Treatment: Patients will continue to be enrolled into both cohorts based on their tumor specificities with a total of 31 patients in Cohort 1 (ER-/PR-/HER2-/AR+) and 55 patients in Cohort 2 (ER+ and/or PR+/AR+). Patients will be evaluated every eight weeks for response to treatment. All patients who respond to treatment (complete response [CR] or partial response [PR]) or have stable disease (SD) will continue to receive orteronel until they develop progressive disease (PD) or unacceptable toxicity.
Study Drug(s), Dose, and Mode of Administration:	Orteronel will be supplied to SCRI Innovations by Millennium Pharmaceuticals, Inc. The planned oral dose of orteronel is 300 mg BID. In the event of prohibitive toxicity, the orteronel dose may be reduced by one level to 200 mg BID.
Inclusion Criteria:	1. Voluntary written informed consent before performance of any study-related procedure not part of normal medical care 2. Patients must have MBC that is measurable or evaluable as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria (see Section 9). Patients with metastases limited to the bones are eligible. 3. Patients with breast tumors that are AR+ (≥10% staining by immunohistochemistry). Archived tumor tissue from a primary biopsy or metastatic lesion for centralized determination of AR expression is mandatory. If tissue is limited, the additional correlative testing is optional. If tissue is not available, a patient will not be eligible for enrollment into the study. Patients may enroll based on local laboratory AR assessment, but will need to submit tissue for confirmation at the central laboratory. 4. In addition to having AR+ tumors, patients must fit into 1 of the 2 following categories: • Triple negative (ER-/PR-/HER2-) (*Note: This group of patients must have received at least 1 and up to 3 prior chemotherapy regimens in the advanced setting.*) • ER+ and/or PR+ (*Note: This group of patients must have received at least 1 and up to 3 prior hormonal therapies and at least one prior chemotherapy treatment in the advanced setting. HER2+ patients in this group must have received a minimum of 2 lines of HER2-directed therapy in the advanced setting.*) This group of patients may be pre-menopausal with ovarian suppression or post-menopausal. LHRH agonists maybe used to render ovarian suppression with post-menopausal ranges of estradiol or FSH per institutional guidelines. 5. Female or male patients ≥18 years-of-age 6. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 (see Appendix A) 7. Patient has recovered (to Grade ≤1) from all clinically significant toxicities related to prior antineoplastic therapies (with the exception of alopecia) 8. Adequate hematological function, defined as: • Absolute neutrophil count (ANC) ≥1.25 x 10^9/L • Platelets ≥75 x 10^9/L • Hemoglobin ≥9 g/dL 9. Adequate liver function, defined as: • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN), if no liver involvement or ≤5 x ULN with liver involvement • Total bilirubin ≤1.5 times the upper limit of normal (ULN) (in patients with known Gilbert Syndrome, a total bilirubin ≤3.0 x ULN, with direct bilirubin ≤1.5 x ULN)

Inclusion Criteria (continued):	10. Adequate renal function, defined as: • Creatinine ≤1.5 x ULN or creatinine clearance ≥40 mL/min as calculated by the Cockcroft-Gault method 11. Screening calculated LVEF of ≥50% by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan 12. Ability to swallow and retain oral medication 13. Male patients (even those post vasectomy) who are willing to use adequate contraceptive measures (see Appendix B) or abstain from heterosexual intercourse during the entire study treatment period and for 4 months after the last dose of study drug 14. Female patients who are not of child-bearing potential and female patients of child-bearing potential who agree to use adequate contraceptive measures (see Appendix B) or abstain from heterosexual intercourse during the entire study treatment period and for 4 months after the last dose of study drug, who are not breastfeeding, and who have had a negative serum/urine pregnancy test ≤7 days prior to dosing 15. Life expectancy of ≥3 months 16. Willingness and ability to understand the nature of this study and to comply with the study and follow-up procedures.
Exclusion Criteria:	1. Known hypersensitivity to orteronel or to orteronel excipients, which are listed by formulation in the Investigator Brochure 2. Patients receiving other treatment for breast cancer (includes standard hormonal therapy, chemotherapy, biologic therapy, immunotherapy, or radiation therapy). Patients receiving chronic bisphosphonate or denosumab therapy are eligible. 3. Female patients who are both lactating and breastfeeding or have a positive serum pregnancy test during the screening period. 4. Prior anti-androgen therapy 5. Use of an investigational drug ≤21 days or 5 half-lives (whichever is shorter) prior to the first dose of orteronel, or concurrent treatment. For investigational drugs for which 5 half-lives is less than 21 days, a minimum of 10 days between termination of the investigational drug and administration of orteronel is required. 6. Active brain metastases or leptomeningeal disease. Previously treated brain metastases are allowed provided lesions are stable for at least 3 months as documented by head CT scan or magnetic resonance imaging (MRI) of the brain. Patients must be off steroids, but anti-convulsants are allowed. 7. Patients with known adrenal insufficiency, or patients receiving treatment with ketoconazole, abiraterone, or aminoglutethimide. 8. Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days prior to starting study drug or has not recovered from side effects of such therapy. 9. Major surgical procedures ≤28 days of beginning study treatment or minor surgical procedures ≤7 days. No waiting is required following port-a-cath placement. 10. Presence of active gastrointestinal (GI) disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (eg, ulcerative disease, uncontrolled nausea, vomiting, diarrhea ≥ Grade 2, and malabsorption syndrome).

Exclusion Criteria: (continued)	11. History of myocardial infarction, unstable symptomatic ischemic heart disease, ongoing arrhythmias > Grade 2 (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.0), thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events), or any other cardiac condition (eg, pericardial effusion restrictive cardiomyopathy) within 6 months prior to first dose of study drug. Chronic stable atrial fibrillation on stable anticoagulant therapy is allowed. 12. New York Heart Association (NYHA) Class III or IV heart failure (Appendix C) 13. Electrocardiogram (ECG) abnormalities of Q-wave infarction, unless identified 6 or more months prior to screening or QTc Fridericia (F) interval >460 msec 14. Inadequately controlled hypertension (ie, systolic blood pressure [SBP] >160 mmHg or diastolic BP [DBP] >90 mmHg) at 2 separate measurements no more than 60 minutes apart during the Screening visit. Note: patients may be rescreened after adjustment of antihypertensive medications. 15. Known diagnosis of human immunodeficiency virus, active chronic hepatitis B, or C, life-threatening illness unrelated to cancer, or any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with participation in this study 16. Uncontrolled diabetes mellitus. Patients with Type II diabetes are eligible if they require only oral hypoglycemic agents and fasting blood glucose level is ≤120. Patients with Type I diabetes are eligible if their glycosylated hemoglobin (HbA_{1c}) is ≤7. 17. Diagnosis or treatment for another malignancy within 2 years of enrollment, with the exception of adequately treated in-situ carcinoma of the cervix, uteri, basal or squamous cell carcinoma or non-melanomatous skin cancer 18. Inability or unwillingness (including psychological, familial, sociological, or geographical conditions) to comply with study and/or follow-up procedures as outlined in the protocol. 19. Use of a prohibited concomitant medication (see Section 5.3.2 and Appendix D) that cannot be safely discontinued or substituted.
Correlative Testing:	The following correlative testing will included: • Measurement of changes in serum estradiol levels, total and free testosterone levels, and SHBG • Measurement of changes in ACTH, DHEA-S, and cortisol levels • Biomarker testing of archived tumor tissue for loss of PTEN and PIK3CA mutations.

Statistical Methodology:	For patients with ER-/PR-/HER2-/AR+ tumors (Cohort 1), the expected response rate with standard anti-estrogen therapy is expected to be zero. Therefore, a response rate of at least 10% with orteronel therapy would indicate activity and would lead to further investigation. Assuming an evaluable population of 28 patients, the exact 95% confidence intervals (CIs) for a hypothesized response rate of 11% is (2.4%, 28.6%). In order to incorporate an early stopping rule, Simon's two-stage design is applied using alpha = 0.10 and power = 0.80 with comparison of the hypothesized response rate of 11% versus a conservative value of 2%. Initially, 19 patients will be enrolled in this cohort, and if no responses are observed, recruitment to this cohort will stop. Otherwise, enrollment in this cohort will continue to full accrual of 28 patients. To account for an unevaluable rate of 10%, a total of 31 patients will be enrolled in this cohort. For patients with ER+ and/or PR+/AR+ tumors (Cohort 2), published data on exemestane as third-line hormonal therapy in postmenopausal women indicate a response rate of 13% and a clinical benefit rate (CR, PR, or SD >24weeks) of 30%. It is hypothesized that treatment with orteronel in this patient population will produce similar results. Assuming an evaluable population of 50 patients, the exact 95% CIs for a hypothesized response rate of 14% is (5.8%, 26.7%). In order to incorporate an early stopping rule, Simon's two-stage design is applied using alpha = 0.10 and power = 0.80 with comparison of the hypothesized response rate of 14% versus a conservative value of 5.1%. Initially, 26 patients will be enrolled in this cohort, and if one or no responses are observed, recruitment into this cohort will stop. Otherwise, enrollment in this cohort will continue to full accrual of 50 patients. To account for an unevaluable rate of 10%, a total of 55 patients will be enrolled in this cohort.

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List of Abbreviations

ACTH	adrenocorticotropic hormone
ADL	activity of daily living
AKT	protein kinase B
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
AR (+)	androgen receptor (positive)
AST	aspartate aminotransferase
BP	blood pressure
BID	twice daily
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CMP	comprehensive metabolic profile
CR	complete response
CRPC	castration-resistant prostate cancer
eCRF	electronic case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
DCR	disease control rate
DDI	drug-drug interactions
DHEA-S	dehydroepiandrosterone sulfate
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
ER+ or -	estrogen receptor positive or negative
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HbA_{1c}	glycosylated hemoglobin
HER2–	human epidermal growth factor receptor 2 negative
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LAR	luminal androgen receptor
LFT	liver function tests
LVEF	left ventricular ejection fraction
MBC	metastatic breast cancer
MRI	magnetic resonance imaging
MUGA	multi-gated acquisition scan

List of Abbreviations (Continued)

NYHA	New York Heart Association
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI	Principal Investigator
PI3K	phosphatidylinositol 3-kinase
PO	*per os* (orally, by mouth)
PR	partial response
PR+ or -	progesterone receptor positive or negative
PTEN	phosphatase and tensin homolog
PSA	prostate specific antigen
QA	quality assurance
RECIST	Response Evaluation Criteria in Solid Tumors
RR	response rate
SAE	serious adverse event
SBP	systolic blood pressure
SCRI	Sarah Cannon Research Institute
SD	stable disease
SHBG	sex hormone binding globulin
TNBC	triple-negative breast cancer
ULN	upper limit of normal

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1. INTRODUCTION

1.1. Background

The androgen receptor (AR) is expressed in 70% to 90% of primary breast tumors and in 75% of breast cancer metastases. It is the sole sex steroid receptor expressed in 35% of metastases (Birrell et al. 1998).

Triple-negative breast cancer (TNBC), which is estrogen-receptor negative (ER-), progesterone-receptor negative (PR-), and human epidermal-growth-factor-receptor-2 negative (HER2-) constitutes 20% of all new breast cancers diagnosed. The patients who experience this disease do not benefit from standard hormone or HER2-targeted therapies, and there are no optimal standard treatment regimens for the management of metastatic TNBC.

Although survival is more favorable in the ER+ group of patients, there are few non-toxic treatments available once anti-estrogen therapies are exhausted. Hence, there is an impetus to develop novel hormonal agents in refractory metastatic breast cancer (MBC). Clinical interest is currently being directed to the role of the AR as a potential therapeutic target for treatment of MBC in the ER-/AR+ and the ER+/AR+ subsets of patients (Gucalp and Traina, 2010).

The effects of androgen inhibition and stimulation on ER+/AR+ cancers are variable. Approximately 30% of patients with refractory MBC will respond to androgen therapy. It is clear that androgens do not always act as growth promoters in breast cancer in the same ways that estrogens do. In fact, preliminary work has shown that, for estrogen-dependent growth in a cancer cell, there is a functional interaction of ER and AR signaling. Certain cell lines, when given testosterone, show inhibition of ER activity in a dose-dependent fashion. Also, when a constitutively active AR is introduced to certain cell lines (T-47D), estrogen-induced proliferation is inhibited. It is thought that this AR is recruited to specific estrogen response elements and prevents activation of target genes that mediate stimulatory effects of estrogen on breast cancer cells (Gucalp and Traina, 2010). In other breast cancer cell lines, androgens have been shown to promote growth and proliferation. MCF 7 cells (ER+/PR+ and AR+) and MDA-MB453 cells (ER-/PR- and AR+) are both stimulated by androgens *in vitro* (Birrell et al. 1998). We hypothesize that patients with breast cancers expressing similar receptor profiles might respond when androgen levels are lowered by blockade of adrenal androgen synthesis.

1.2. Orteronel

Orteronel, a novel, orally active, selective, nonsteroidal inhibitor of 17, 20-lyase, is being developed as an endocrine therapy for relevant hormone-sensitive cancers such as prostate cancer and breast cancer. Orteronel is expected to suppress sex hormone levels in both circulation and relevant hormone-dependent malignant tissue.

1.2.1. Summary of Non-clinical Findings

In vitro and *in vivo* pharmacology studies indicate that orteronel is a reversible inhibitor of human and monkey 17,20-lyase activity. Absorption, distribution, metabolism, and excretion (ADME) studies, showed that the bioavailability of orteronel in rats and monkeys was 41.0% and 70.5%, respectively. ^{14}C-labeled parent compound and metabolites were distributed widely into

the tissues of male and female rats, with relatively high concentrations in the liver and adrenal gland. Orteronel is metabolized into M-I (also known as M1) via hydrolysis of the amide bond and other minor metabolites via lucuronidation of both orteronel and M-I (in human plasma samples). Additionally, T-1358043 (TAK-700 dehydrate) is a minor metabolite of orteronel that is also a process impurity and drug product degradant. *In vitro* testing demonstrated minimal involvement of cytochrome P450 (CYP) isozymes in the metabolism of orteronel. Orteronel is not an inducer of CYP2B6 and 3A4/5, but is a moderate inducer of CYP1A2. Based on the results of CYP isozyme and transporter inhibition studies, orteronel is unlikely to cause CYP isozyme- or transporter-mediated drug-drug interactions (DDIs). In addition, a physiologically based pharmacokinetic DDI modeling study showed that orteronel, as an inhibitor, is unlikely to cause CYP isozyme-mediated clinical DDI. Orteronel and its metabolites were eliminated primarily in the feces in rats and urine in monkeys.

The safety of orteronel has been assessed in a battery of single and repeat-dose oral (PO) toxicity studies in mice, rats, dogs, and/or monkeys; reproductive toxicity studies in rats and rabbits; and genotoxicity studies; as well as additional toxicology studies with T-1358043. Effects noted in toxicology studies were consistent with the pharmacologic inhibition of 17,20-lyase activity and included atrophy of the epididymis, prostate, and seminal vesicle; delay in the development of spermatogenesis; increased fetal mortality; and decreased fetal weights. In chronic 6-month rat and 9-month monkey toxicity studies, the no observed adverse effect levels (NOAELs) were 3 and 1 mg/kg, respectively, which corresponded with area under the concentration-versus-time curves (AUC) from 0 to 24 hours ($AUC_{0\text{-}24hr}$) values of 1649 and 1016 hr*ng/mL in males, respectively.

Orteronel itself was not mutagenic or clastogenic in genotoxicity tests and did not elicit changes indicative of cutaneous or ocular phototoxicity. However, T-1358043 was positive for genotoxicity *in vitro* and when dosed neat, positive for genotoxicity in Muta™Mice dosed with T-1358043 at ≥15 mg/kg (mean T-1358043 $AUC_{0\text{-}24hr}$ of 7950 hr*ng/mL). However, T-1358043 was negative for genotoxicity when dosed at 5 mg/kg ($AUC_{0\text{-}24hr}$ of 1050 hr*ng/mL) in Muta™Mice. Therefore, T-1358043 could potentially pose a risk to human subjects by leading to a secondary malignancy if plasma exposure in humans approaches the levels noted at 15 mg/kg in the Muta™Mice. The mean T-1358043 AUC values in the Muta™Mouse study at the no observed effect level (5 mg/kg) were approximately 7 times greater than the estimated mean steady-state level of T-1358043 formed in patients with CRPC administered the clinical dose of 400-mg orteronel PO twice daily (BID) in Study C21003.

For a complete discussion of the nonclinical data, please refer to the TAK-700 Investigator's Brochure (IB).

1.2.2. Summary of Clinical Findings

Based on the clinical development experience to date, the overall risk/benefit of orteronel therapy in patients with CRPC is favorable. For the most current summary of the studies conducted to date, please refer to the current IB.

The most commonly reported treatment-emergent adverse events (TEAEs) in patients enrolled in orteronel clinical studies include fatigue, nausea, constipation, diarrhea, and headache. Typical

adverse events (AEs) associated with androgen-deprivation therapy and with orteronel can be monitored and managed with supportive care or dose modification.

Orteronel has dose-proportional, single-dose and multiple-dose pharmacokinetics (PK). Excretion of parent drug and M-I occurs primarily via the kidney. The steady state PK profile of orteronel administered twice daily allows for fairly consistent inhibition of adrenal androgen and testosterone production throughout the day.

Review of the available nonclinical pharmacology and toxicology findings, the Phase I clinical data in healthy male subjects and the Phase 1 through 2 clinical data in men with CRPC supports the continued clinical development of orteronel for the treatment of CRPC. Phase III clinical studies are ongoing to further evaluate the safety and efficacy of orteronel in this population.

1.2.2.1. Identified and Potential Risks with Orteronel

Single and multiple doses of orteronel up to 600 mg appeared to be safe and well tolerated in Phase II studies conducted in healthy male subjects. The most common AE observed in the completed Phase I studies in healthy subjects was headache.

Orteronel appears to have an acceptable tolerability profile in patients with prostate cancer, across all doses tested thus far. The most commonly reported TEAEs are fatigue, nausea, constipation, diarrhea, and headache.

Other identified risks associated with orteronel treatment include:

- Effects of androgen deprivation
- Left ventricular ejection fraction (LVEF) decreased
- Adrenal insufficiency
- Compensatory elevated adrenocorticotropic hormone concentrations, which may result in increased mineralocorticoid activity
- Hepatotoxicity
- Genotoxicity, that could potentially lead to carcinogenesis and second malignancies

For a complete discussion of the safety data, please refer to the current IB.

1.3. Rationale for the Study

To date, there have been no investigations of Orteronel in AR+ patients with MBC. However, preliminary results of a Phase I study with abiraterone acetate (an inhibitor of adrenal androgen synthesis, similar to orteronel), including 25 patients with MBC expressing ER+ or ER-/AR+, were encouraging and toxicities were manageable (Basu et al. 2011). Although the median time on treatment was short for this group of patients with resistance to at least 2 prior hormone therapies, two patients (both ER+/AR+) continued on treatment beyond 11 months (Basu et al. 2011). There are also positive preliminary results in an ongoing study of bicalutamide, a non-steroidal anti-androgen that competitively inhibits AR, in patients with ER-/PR-/AR+ tumors (Traina et al. 2009, Gucalp et al. 2012).

In addition, Lehmann et al. have recently identified a luminal androgen receptor (LAR) subtype, one of six distinct subsets of TNBC identified by transcriptome analysis (Lehmann et al. 2011). *In vitro* and *in vivo* assays have shown the LAR subtypes to be sensitive to bicalutamide, a potent anti-androgen. Therefore, TNBC patients with AR expression could potentially benefit from effective anti-androgen therapy like orteronel.

Substantial evidence therefore suggests that the AR is a potential therapeutic target in selected patients with MBC. Two subsets of patients with MBC will be studied separately in this study:

- ER-/PR-/HER2-/AR+
- ER+ and/or PR+/AR+

This trial will be conducted in accordance with the International Conference on Harmonization (ICH) guideline on Good Clinical Practice (GCP) (E6), Title 21 of the Code of Federal Regulations (CFR) parts 50, 54, 56, and 312, and any other applicable local regulatory requirements.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objectives of this study are to evaluate:

- Response rate (RR) and disease control rate (DCR) following treatment with orteronel in patients with refractory metastatic triple-negative breast cancer expressing AR (ER-/PR-/HER2-/AR+)
- Response rate and disease control rate (DCR) following treatment with orteronel in patients with refractory ER+ and/or PR+/AR+ breast cancer.

2.2. Secondary Objectives

The secondary objectives of this study are to evaluate:

- Safety and tolerability of the regimen
- Measurement of changes in serum estradiol levels, total and free testosterone levels, and sex hormone binding globulin (SHBG) during treatment with orteronel
- Measurement of changes in ACTH, DHEA-S, and cortisol levels during treatment with orteronel
- Progression-free survival (PFS)
- Overall survival (OS)

2.3. Exploratory Objective

As an exploratory objective of this trial:

- Archived tumor tissue will be assayed for the following biomarkers: loss of phosphatase and tensin homolog (PTEN) and phosphatidylinositol 3-kinase (PIK3CA) mutations.

3. STUDY PATIENT POPULATION AND WITHDRAWAL

This study will enroll patients with MBC who have progressed on prior hormonal/ chemotherapy regimens and whose cancer expresses AR. Patients will be enrolled onto one of the 2 following cohorts based on their tumor specificity:

- Cohort 1: Patients with estrogen receptor negative (ER-)/ progesterone receptor negative (PR-)/ human epidermal growth factor receptor 2 negative (HER2-)/AR positive (+) MBC with 1 to 3 previous treatments for metastatic disease
- Cohort 2: Postmenopausal women with ER+ and/or PR+/AR+ refractory MBC who have progressed after at least one, and up to 3, previous hormonal treatments for metastatic disease.

3.1. Inclusion Criteria

Patients must meet the following criteria in order to be included in this clinical study:

1. Voluntary written informed consent before performance of any study-related procedure not part of normal medical care
2. Patients must have MBC that is measurable or evaluable as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria (see Section 9). Patients with metastases limited to the bones are eligible.
3. Patients with breast tumors that are AR+ (>10% staining by immunohistochemistry). Archived tumor tissue from a primary biopsy or metastatic lesion for centralized determination of AR expression is mandatory. If tissue is limited, the additional correlative testing is optional. If tissue is not available, a patient will not be eligible for enrollment into the study. Patients may enroll based on local laboratory AR assessment, but will need to submit tissue for confirmation at the central laboratory.
4. In addition to having AR+ tumors, patients must fit into 1 of the 2 following categories:
    - Triple negative (ER-/PR-/HER2-) *Note: This group of patients must have received at least 1 and up to 3 prior chemotherapy regimens in the advanced setting.*
    - ER+ and/or PR+ *Note: This group of postmenopausal patients must have received at least 1 and up to 3 prior hormonal therapies and at least one prior chemotherapy treatment in the advanced setting. HER2+ patients in this group must have received a minimum of 2 lines of HER2-directed therapy in the advanced setting*. This group of patients may be pre-menopausal with ovarian suppression or post-menopausal. LHRH agonists maybe used to render ovarian suppression with post-menopausal ranges of estradiol or FSH per institutional guidelines.
5. Female or male patients ≥18 years-of-age

6. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 (see Appendix A)
7. Patient has recovered (to Grade ≤1) from all clinically significant toxicities related to prior antineoplastic therapies (with the exception of alopecia)
8. Adequate hematological function, defined as:
    - Absolute neutrophil count (ANC) ≥1.25 x 10^9/L
    - Platelets ≥75 x 10^9/L
    - Hemoglobin ≥9 g/dL
9. Adequate liver function, defined as:
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN), if no liver involvement or ≤5 x ULN with liver involvement
    - Total bilirubin ≤1.5 times the upper limit of normal (ULN) (in patients with known Gilbert Syndrome, a total bilirubin ≤3.0 x ULN, with direct bilirubin ≤1.5 x ULN)
10. Adequate renal function, defined as:
    - Creatinine ≤1.5 x ULN or creatinine clearance ≥40 mL/min, as calculated by the Cockcroft-Gault method
11. Screening calculated LVEF of ≥50% by echocardiogram (ECHO) or by multiple-gated acquisition (MUGA) scan
12. Ability to swallow and retain oral medication
13. Male patients, even post vasectomy, who are willing to use adequate contraceptive measures (see Appendix B) or abstain from heterosexual intercourse during the entire study treatment period and for 4 months after the last dose of study drug
14. Female patients who are not of child-bearing potential and female patients of child-bearing potential who agree to use adequate contraceptive measures (see Appendix B) or abstain from heterosexual intercourse during the entire study treatment period and for 4 months after the last dose of study drug, who are not breastfeeding, and who have had a negative serum/urine pregnancy test ≤7 days prior to dosing
15. Life expectancy of ≥3 months
16. Willingness and ability to understand the nature of this study and to comply with the study and follow-up procedures.

3.2. Exclusion Criteria

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

1. Known hypersensitivity to orteronel or to orteronel excipients, which are listed by formulation in the IB
2. Patients receiving other treatment for breast cancer (includes standard hormonal therapy, chemotherapy, biologic therapy, immunotherapy, or radiation therapy). Patients receiving chronic bisphosphonate or denosumab therapy are eligible.
3. Female patients who are both lactating and breastfeeding or have a positive serum/urine pregnancy test during the screening period.
4. Prior anti-androgen therapy
5. Use of an investigational drug ≤21 days or 5 half-lives (whichever is shorter) prior to the first dose of orteronel, or concurrent treatment. For investigational drugs for which 5 half-lives is less than 21 days, a minimum of 10 days between termination of the investigational drug and administration of orteronel is required.
6. Active brain metastases or leptomeningeal disease. Previously treated brain metastases are allowed provided lesions are stable for at least 3 months as documented by head CT scan or magnetic resonance imaging (MRI) of the brain. Patients must be off steroids, but anti-convulsants are allowed.
7. Patients with known adrenal insufficiency, or patients receiving treatment with ketoconazole, abiraterone, or aminoglutethimide.
8. Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days prior to starting study drug or has not recovered from side effects of such therapy.
9. Major surgical procedures ≤28 days of beginning study treatment or minor surgical procedures ≤7 days. No waiting is required following port-a-cath placement.
10. Presence of active gastrointestinal (GI) disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (eg, ulcerative disease, uncontrolled nausea, vomiting, diarrhea ≥ Grade 2, and malabsorption syndrome).
11. History of myocardial infarction, unstable symptomatic ischemic heart disease, ongoing arrhythmias > Grade 2 (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.0), thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events), or any other cardiac condition (eg, pericardial effusion restrictive cardiomyopathy) within 6 months prior to first dose of study drug. Chronic stable atrial fibrillation on stable anticoagulant therapy is allowed.
12. New York Heart Association (NYHA) Class III or IV heart failure (Appendix B)

13. Electrocardiogram (ECG) abnormalities of:
    - Q-wave infarction, unless identified 6 or more months prior to screening
    - QTc Fridericia (F) interval > 460 msec
14. Inadequately controlled hypertension (ie, systolic blood pressure [SBP] >160 mmHg or diastolic BP [DBP] >90 mmHg) at 2 separate measurements no more than 60 minutes apart during the Screening visit. Note: patients may be rescreened after adjustment of antihypertensive medications.
15. Known diagnosis of human immunodeficiency virus, active chronic hepatitis B, or C, life-threatening illness unrelated to cancer, or any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with participation in this study
16. Uncontrolled diabetes mellitus. Patients with Type II diabetes are eligible if they require only oral hypoglycemic agents and fasting blood glucose level is ≤120. Patients with Type I diabetes are eligible if their glycosylated hemoglobin (HbA_{lc}) is ≤7.
17. Diagnosis or treatment for another malignancy within 2 years of enrollment, with the exception of adequately treated in-situ carcinoma of the cervix, uteri, basal or squamous cell carcinoma or non-melanomatous skin cancer
18. Inability or unwillingness (including psychological, familial, sociological, or geographical conditions) to comply with study and/or follow-up procedures as outlined in the protocol.
19. Use of a prohibited concomitant medication (see Section 5.3.2 and Appendix D) that cannot be safely discontinued or substituted.

3.3. Discontinuation from Study Treatment

Patients will be discontinued from study treatment for any of the following reasons:

- Disease progression
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Patient requests to withdraw from the study and discontinue treatment
- Patient requests to discontinue treatment
- Pregnancy
- Inability of the patient to comply with study requirements
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the investigator's discretion)
- Non-compliance/lost to follow-up.

After withdrawal from protocol treatment, patients must be followed for AEs for 30 calendar days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patients' medical records and as a comment on the electronic Case Report Form (eCRF).

All patients who have Grade 3 or 4 laboratory abnormalities (CTCAE, Version 4.0) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the investigator, not likely that these values are to improve. In this case, the investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment on the eCRF.

3.4. Pregnancy

Male patients, even if surgically sterilized, and female patients of child-bearing potential must:

- Agree to practice effective barrier contraception during the entire study treatment period and for 4 months after the last dose of study drug, or
- Agree to completely abstain from heterosexual intercourse.

During the course of the study, all female patients of childbearing potential (the definitions of "women of childbearing potential" are listed in Appendix B) must contact the treating investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating investigator), despite following the precautions listed above.

If an investigator suspects that a patient may be pregnant prior to administration of study drug, the study drug must be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the patient must not receive any study drug, and must be discontinued from the study.

If an investigator suspects that a patient may be pregnant after the patient has been receiving study drug, the study drug must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the study drug must be immediately and permanently stopped, the patient must be discontinued from the study, and the investigator must notify the Medical Monitor as soon as possible. If a patient becomes pregnant while enrolled in the study, a Pregnancy Form (a paper report form) should be completed and faxed to SCRI Innovations Safety Department. For more details regarding handling and reporting of pregnancies that occur during treatment, see Section 11.5.

4. STUDY REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks and discomforts. Human protection committee approval of this protocol and informed consent form are required.

Patients will sign a pre-screen informed consent form (ICF) for centralized determination of AR expression in an archived tumor sample from a primary biopsy or metastatic lesion. Patients whose tumors have an AR expression ≥10% will then sign and date the main ICF and will be screened to determine eligibility for enrollment into the study. Eligible patients who wish to participate in the study will be enrolled into the study. Patients with ≥10% AR expression in their tumor tissue based on local lab assessment may enroll on the study, but will be required to provide tumor tissue for confirmation at the central laboratory.

Registration must occur prior to the initiation of protocol therapy. Patients eligible to participate in the study may be enrolled through the SCRI Innovations by calling (877) MY-1-SCRI. Registration may be done via fax (866) 699 0258 Monday through Friday, 8:30 a.m. to 4:30 p.m., Central Standard Time. Patient registration will be confirmed within 24 hours, or by the next business day.

5. STUDY DESIGN

This is an open-label, multicenter, Phase II study to be conducted in 2 stages. All patients will receive orteronel PO at a dose of 300 mg twice daily (BID) (600 mg total daily dose).

- Lead-in Phase: The first 6 patients treated will be evaluated every week to confirm the safety and feasibility of this regimen. After all 6 patients complete at least 4 weeks of treatment, and if no prohibitive toxicities are identified, continuous study treatment will begin.
- Continuous Study Treatment: Patients will continue to be enrolled into both cohorts based on their tumor specificities up to a total of 31 patients in Cohort 1 (ER-/PR-/HER2-/AR+) and 55 patients in Cohort 2 (ER+ and/or PR+/AR+). These numbers include the patients that are participating in the lead-in phase.

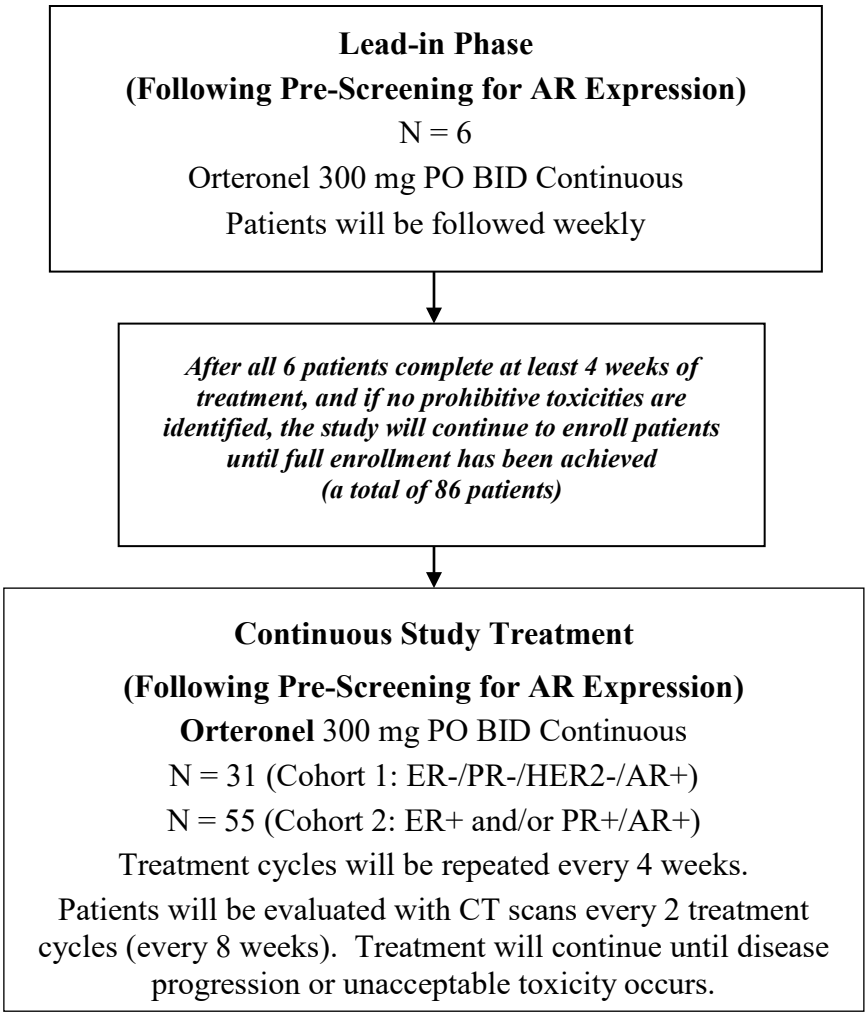
Up to 86 patients are planned to be enrolled in this study (6 for the lead-in phase and 80 for continuous study treatment).

Patients will be evaluated every eight weeks for response to treatment.

All patients who respond to treatment (complete response [CR] or partial response [PR]) or have stable disease (SD) will continue to receive orteronel until they develop progressive disease (PD) or unacceptable toxicity.

The study design schema is presented in Figure 1.

Figure 1. BRE 203 Treatment Schema



5.1. Treatment Plan

All patients entering this study will receive continuous 300 mg orteronel PO BID as monotherapy. In the event of prohibitive toxicity, the orteronel dose may be reduced by one level to 200 mg BID.

5.2. Correlative Studies

The PI3Ks are a family of lipid kinases that regulate an intracellular signal transduction network, which in turn controls many features of cell behavior including growth, survival, motility, metabolism, and additional specialized functions. Several activating mutations in the PIK3CA gene encoding p110 alpha have been identified. In addition, the PI3K pathway is activated in

cancers with mutations causing inactivation or silencing of the PTEN, a tumor suppressor gene. Breast cancers frequently harbor molecular/genomic aberrations that increase activation of the PI3K signaling pathway including loss of PTEN function or activating PIK3CA mutations (Engelman, 2009). Recent studies have found that AR is expressed in 60% to 70% of breast cancers regardless of ER status (Niemeier et al. 2010). Studies have also shown that there were significant differences in AR expression levels by PIK3CA mutation status (Gonzalez-Angulo et al. 2009). Interestingly, prostate cancer is characterized by its dependence on AR and frequent activation of PI3K signaling. A recent study has shown that these two oncogenic pathways cross-regulate each other by reciprocal feedback. Inhibition of one activates the other, thereby maintaining tumor cell survival (Carver et al. 2011). We proposed to test the PIK3CA mutation status and PTEN loss in patients in this study to investigate whether the activation of PI3K pathway correlates with the response to orteronel treatment.

PIK3CA mutation at codons 88, 539-549, 1020-1025, 1043-1049 will be tested by pyrosequencing and the results will be signed off by a molecular pathologist. PTEN loss will be determined by immunohistochemical staining using Ventana systems and the report will be signed off by a pathologist. Both assays will to be performed at a CLIA/CAP certified lab. These analyses are exploratory, and will not be used to guide treatment decisions.

5.2.1. Blood samples for measuring serum hormone levels

Blood samples will be collected at baseline, on Cycle 2 Day 1, on Cycle 4 Day 1, and at the End-of-Treatment Visit to test for serum levels of estradiol, total and free testosterone, SHBG, ACTH, DHEA-S, and cortisol. A blood sample will be collected for this purpose from each patient at the noted time points (see Appendix E) and submitted to a laboratory for testing. Details of the laboratory will be provided to the site by the study team. When the results are received by the site, they will be entered into the appropriate eCRF page.

5.3. Concomitant Medications

Patients will be instructed not to take any additional medications during the course of the study without prior consultation with the research team. At each visit, the patient will be asked about any new medications he/she is taking or has taken after the start of the study drug.

5.3.1. Permitted Concomitant Medications

- Use of erythropoietin replacement or bisphosphonates or denosumab is considered supportive care, and their use **is** permitted, if initiated >2 weeks prior to study treatment.
- Patients are permitted to receive palliative radiation therapy on study to pre-existing, symptomatic lesions at the discretion of the treating physician.

All other drugs are allowed with the exception of those listed in Section 5.3.2.

5.3.2. Prohibited Concomitant Medications

The following treatments are prohibited while in this study:

- Other investigational drug treatments or study participation
- Other treatment for breast cancer including hormonal therapy, chemotherapy, biologic therapy, immunotherapy, or radiation therapy (except as described in Section 5.3.1). Specific excluded hormonal therapies include estrogens, progestins, or herbal products. Patients with HER2+ tumors should have completed trastuzumab therapy.
- Concomitant treatment with any medication that may cause QT prolongation or Torsade*s* de Pointes (see Appendix D). If a patient, after study enrollment, requires use of a medication that may cause QT prolongation and/or Torsades de Pointes that cannot be safely substituted, the patient must be removed from the study.
- Ketoconazole
- Aminoglutethimide
- Abiraterone (Zytiga®)
- Enzalutamide (MDV-3100)
- 5-alpha reductase inhibitors (eg, finasteride or dutasteride)
- Chronic systemic corticosteroids. If mineralocorticoid-related AEs occur and cannot be managed by supportive care (e.g., potassium, antihypertensives) and/or dose modification, low-dose corticosteroids (≤20 mg/day prednisone or its equivalent) can be given at the discretion of the investigator.
- Over-the-counter products such as vitamins, minerals, herbal preparations/medications and other dietary supplements are not allowed throughout the study; over-the-counter multivitamins without antioxidants are allowed. Patients should stop using these herbal medications at least 7 days prior to the first dose of study drug.

6. DOSE MODIFICATIONS

Toxicity will be assessed utilizing the NCI CTCAE v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE), unless otherwise specified.

6.1. Dose Modifications and Reductions

Orteronel, at the dose used in this protocol, is expected to be well tolerated. Substantial acute toxicities should be managed as medically indicated and with temporary suspension of study drug, as appropriate. Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician. For each patient, a maximum of 1 dose reduction will be allowed. The reduced dose level is presented in Table 1. Should the patient not tolerate the lowest possible dose, he/she must discontinue treatment with orteronel.

Table 1. Orteronel Dose Level Modifications

Dose Level		Orteronel BID/Daily
Starting Dose Level	0	300 mg/ 600 mg
Reduced Dose Level	-1	200 mg/ 400 mg

6.1.1. Criteria for Orteronel Dose Reduction

Sections 6.1.1.1 and 6.1.1.2 give management guidelines for treatment-related Grade 2, 3, and 4 toxicities. Subsequent sections present additional details regarding management of specific toxicities (Sections 6.1.3.1 through 6.1.3.8).

6.1.1.1. Grade 3 and 4 Toxicities

Dose modifications for acute renal insufficiency and abnormal liver function tests are presented separately in Sections 6.1.3.7 and 6.1.3.8, respectively.

Grade 4 non-hematologic toxicity: Discontinue orteronel

Grade 3 toxicities:

Grade 3 AEs that are considered at least possibly related to study drug require a dosing hold for a minimum of 2 weeks.

Once the dose is reduced, reassessment is required at least every 2 weeks until the event is resolved or stabilized. However, the frequency of reassessment should be increased as clinically indicated. If the grade worsens at any time, the dose should be decreased in accordance with the guidelines for the worst grade.

After the toxicity has improved to ≤ Grade 1, orteronel should be restarted with a dose reduction. If the Grade 3 toxicity recurs on the reduced orteronel dose, the drug should be discontinued. Dose reduction for a Grade 3 toxicity is permanent; orteronel should not be re-escalated. Any patient who requires a treatment delay of more than 3 weeks due to treatment-related toxicity will be discontinued from study treatment, unless the treating physician and the Medical Monitor or Study Chair agree that continued treatment at lower doses is in the best interest of the patient.

Asymptomatic Grade 3 or 4 laboratory findings may not require dose modification (ie, dose hold or reduction) especially if these are not considered to be clinically significant or related to study drug. The decision to modify the dose should be based on the investigator's clinical judgment. Dose modifications for Grade 3 hyperglycemia should follow the guidelines in Table 6.

6.1.1.2. Grade 2 Clinically Intolerable Toxicities

Dose modifications for acute renal insufficiency and abnormal liver function tests are presented separately in Sections 6.1.3.7 and 6.1.3.8, respectively.

For a clinically intolerable Grade 2 AE that is considered at least possibly related to study drug, the dose should be decreased by 1 dose level for 2 weeks. The investigator should identify other potential causes of any AE or laboratory abnormality, and consult with the Medical Monitor for any questions regarding the need for dose modification.

Once the dose is reduced, reassessment is required at least every 2 weeks until the event is resolved or stabilized. However, the frequency of reassessment should be increased as clinically indicated.

Subsequent dosing of orteronel should be based on the following guidelines:

- If the AE grade improves to Grade 0 or 1, re-escalate to the full dose (300 mg BID). If the intolerable Grade 2 toxicity recurs, the orteronel dose should be reduced permanently.
- If the AE remains at Grade 2 and is still intolerable after 2 weeks, hold administration of orteronel. If the AE grade improves to ≤ Grade 1 within 3 weeks, and continued treatment is thought to be in the patient's best interest, orteronel may be restarted at the same (reduced) dose.
- If the event worsens to ≥ Grade 3, hold orteronel for 2 weeks followed by a reassessment. If the AE grade improves to ≤ Grade 1 within 3 weeks, and continued treatment is thought to be in the patient's best interest, orteronel may be restarted at the same (reduced) dose.

Reassess the AE after 2 weeks, or sooner, if the AE worsens. Continue to reassess at least every 2 weeks until the event is improved or stabilized. If the dose has been withheld for 3 weeks, orteronel will be discontinued permanently, unless the treating physician and the Medical Monitor or Study Chair agree that continued treatment at the minimum-allowed dose (200 mg BID) is in the best interest of the patient.

6.1.2. Dose Modifications Due to Hematologic Toxicity

It is not expected that the dose will need to be held or modified due to hematologic toxicity in this study. If a Grade 1 or 2 hematologic toxicity does occur, hold orteronel and re-evaluate the patient in 1 week. Absolute neutrophil count and platelets should be monitored weekly until recovery. If ANC and/or platelets do not recover within 3 weeks to ≤ Grade 1, the patient will be discontinued from the study.

6.1.3. Dose Modifications Due to Non-Hematologic Toxicity

Due to its mechanism of action, treatment with orteronel may elicit expression of adverse reactions typically associated with androgen deprivation. Risks associated with androgen deprivation include hot flushes, decreased libido, loss of energy, QTc interval prolongation, or mood swings. Long-term effects of testosterone suppression may also occur, including effects on bone mineral density, muscle mass, hyperglycemia, or lipid or energy metabolism.

Adverse events commonly recorded during clinical trials with orteronel include fatigue, nausea and vomiting, rash, and worsening hypertension. Pancreatitis and/or elevated amylase/lipase have also been reported, occurring in <5% of patients in studies conducted with orteronel.

Pancreatic enzymes will be measured during scheduled serum chemistries for patients receiving long-term administration of orteronel.

For fatigue, mild or intermittent nausea and vomiting, or rash, dose modifications of orteronel should follow the guidelines in Section 6.1.1, depending on the severity.

For ≥ Grade 3 QTc interval prolongation (QTcF >500 ms or >60 ms change from baseline on at least two separate ECGs), orteronel should be held until recovery to ≤ Grade 1 (<480 ms). The patient's chemistries should be checked, as well as concomitant medication usage. Once QTc interval prolongation has resolved, orteronel may be restarted at the reduced dose level. For a second occurrence of ≥ Grade 3 QTc interval prolongation, orteronel should be discontinued.

In the event of any grade 4 non-hematologic toxicity, orteronel should be discontinued.

6.1.3.1. Fatigue

Fatigue is defined as a disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.

Grade 2 to Grade 3 fatigue has occurred in some patients receiving TAK 700 without concomitant prednisone. Less severe Grade 1 or Grade 2 fatigue has been reported in some men receiving concomitant prednisone; other factors such as acute androgen deprivation may also be contributing to symptoms. Table 2 presents the CTCAE Criteria (Version 4.0) for fatigue and the appropriate actions to be followed.

Table 2 CTCAE Criteria and Appropriate Actions for Fatigue

CTCAE Grade	Event Definition	Action Required
1	Fatigue relieved by rest	No action required
2	Fatigue not relieved by rest, limits instrumental Activity of Daily Living (ADL)	Dose modification is optional; If Grade 2 fatigue is intolerable, dose reduction and re-escalation should follow guidelines in Section 6.1.1.2.
3	Fatigue not relieved by rest, limiting self care ADL	Dose reduction follows guidelines in Section 6.1.1.1.

Source: CTCAE Version 4.0
Abbreviations: ADL = activity of daily living

6.1.3.2. Gastrointestinal Adverse Events

Nausea

Nausea is defined as a disorder characterized by a queasy sensation and/or the urge to vomit. Table 3 summarizes the CTCAE Criteria (Version 4.0) for nausea and the appropriate actions to be followed.

Table 3 CTCAE Criteria and Appropriate Actions for Nausea

CTCAE Grade	Event Definition	Action Required
1	Loss of appetite without alteration in eating habits	No action required
2	Oral intake decreased without significant weight loss, dehydration, or malnutrition	Concomitant anti-emetics may initially be administered without dose reduction. If Grade 2 nausea persists and is intolerable, dose reduction and re-escalation should follow Grade 2 Dose Reduction and Dose Re-escalation guidelines
3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	Supportive care regimen should follow local standard of care. Follow Dose Reduction and Dose Re-escalation guidelines

Source: NCI CTCAE Version 4.0

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events; TPN = total parenteral nutrition

Vomiting

Vomiting is defined as a disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth. Table 4 summarizes the CTCAE Criteria (Version 4.0) for vomiting and the appropriate actions to be followed.

Table 4 CTCAE Criteria and Appropriate Actions for Vomiting

CTCAE Grade	Event Definition	Action Required
1	Vomiting 1 to 2 episodes (separated by 5 minutes) in a 24-hour period	No action required
2	Vomiting 3 to 5 episodes (separated by 5 minutes) in a 24-hour period	Concomitant anti-emetics may initially be administered without dose reduction. If Grade 2 vomiting persists and is intolerable, dose reduction should follow Grade 2 Dose Reduction and Dose Re-escalation guidelines
3	Vomiting ≥ 6 episodes (separated by 5 minutes) in a 24-hour period; tube feeding, TPN, or hospitalization indicated	Dose reduction follows Grade 3 Dose Reduction and Dose Re-escalation guidelines
4	Life-threatening consequences; urgent intervention indicated	Discontinue orteronel

Source: CTCAE Version 4.0

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events; TPN = total parenteral nutrition

Note: It is possible that nausea and vomiting could be secondary to acute adrenal insufficiency, e.g., caused by sudden cessation of prednisone dosing. If nausea and vomiting occur in the setting of severe fatigue, prostration, or hypotension, blood should be obtained to check the electrolytes. Institutional standard of care should be followed in the presence of electrolytes imbalance. Even if the vomiting occurs shortly following the study drug dose, no re-dosing of study drug will be done.

Diarrhea

Patients should be treated according to institutional standard of care. Fluid intake should be maintained to avoid dehydration.

Diarrhea is defined as a disorder characterized by frequent and watery bowel movements. Table 5 summarizes the CTCAE Criteria (Version 4.0) for diarrhea and the appropriate actions to be followed.

Table 5 CTCAE Criteria and Appropriate Actions for Diarrhea

CTCAE Grade	Event Definition	Action Required
1	Diarrhea increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	No action needed
2	Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Concomitant anti-diarrheal agents may initially be administered without dose reduction. If Grade 2 diarrhea persists, dose reduction should follow Grade 2 Dose Reduction and Dose Re-escalation guidelines Supportive care regimen should follow local standard of care
3	Increase of ≥ 7 stools per day over baseline; incontinence ~ hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Dose reduction follows Grade 3 Dose Reduction and Dose Re-escalation guidelines
4	Life-threatening consequences; urgent intervention indicated	Discontinue orteronel

Source: CTCAE Version 4.0

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events; TPN = total parenteral nutrition

6.1.3.3. Hyperglycemia

Androgen deprivation has been associated with the new onset of diabetes.

If the patient has a medical history of diabetes mellitus (type I or type II), the patient's diabetes should be followed frequently per local standard of care. A physician experienced in the management of diabetes should be involved in the patient's care. Patients should be counseled for the importance of diet and compliance with diabetic treatment throughout the study; any change in symptoms or home glucose monitoring results should be reviewed at each scheduled visit, and the patient should be encouraged to follow up as required with the physician managing the patient's diabetes. The physician managing the patient's diabetes should be informed whether the patient is on or has recently started any prednisone therapy.

Changes in diabetic medication should be supervised by or be based on consultation with the physician managing the patient's diabetes.

At baseline, if the HbA_{1c} concentration is >7%, the patient should be referred for further assessment to ensure adequate or improved diabetes control while on study. During the study treatment, if there is an increase in HbA_{1c} of 1.5% above baseline or to >8.0%, the patient should be referred to the physician managing the patient's diabetes for additional management support. The management of hyperglycemia or diabetes should be addressed before considering study drug reduction or hold.

Worsening of diabetic control is often associated with acute or chronic infection, other acute illness, new medication (diuretics or beta blockers), or electrolyte abnormalities (hypokalemia). Assessment for these underlying precipitating factors should always be considered in addition to adjusting the diabetes treatment regimen.

Table 6 presents the guidelines that apply to either new onset or previously diagnosed diabetes.

Table 6 CTCAE Criteria and Appropriate Actions for Hyperglycemia

Grade	Event Definition	Action Required
1	Fasting glucose value > 130 up to 160 mg/dL; Fasting glucose value > 6.0 up to 8.9 mmol/L	Review compliance with diabetic medications, check HbA1c. Refer the patient to a physician experienced with management of the diabetes if HbA1c is > 7.0%. No dose modification is required.
2	Fasting glucose value > 160-250 mg/dL; Fasting glucose value > 8.9-13.9 mmol/L	Check HbA1c. If > 7.0%, make sure that the patient is currently under care of a physician experienced with management of the diabetes and refer the patient to that physician for evaluation. Seek precipitating cause(s). Reassess after 2 weeks. No dose modification is required.
3	> 250-500 mg/dL; > 13.9-27.8 mmol/L; hospitalization indicated	Review and assure treatment of precipitating causes, including new infections or hypokalemia. If blood glucose does not improve to Grade ≤ 2, hold orteronel for 2 weeks then reassess. Monitor patient for signs and symptoms of adrenal insufficiency. If the hyperglycemia event was precipitated by a well-defined intercurrent event, orteronel may be resumed at the same dose, if blood glucose improves to Grade ≤2. Otherwise, orteronel should be resumed at the reduced dose (200 mg BID).
4	> 500 mg/dL; > 27.8 mmol/L; life-threatening consequences	Discontinue orteronel.

Source: CTCAE Version 4.0
Abbreviations: BID = twice daily; HbA_{1c} = glycosylated hemoglobin

6.1.3.4. Hypertension

Management of orteronel dosing for different stages of hypertension is outlined in Table 7.

Worsening or new onset hypertension may be part of the natural history of the patients' hypertensive disease, but may also be related to increased adrenal mineralocorticoid activity as a result of increased ACTH secretion induced by relatively nonspecific inhibition of 17-hydroxylase. Reduced potassium or increased serum sodium may be additional indicators of increased mineralocorticoid effect.

If new onset or worsening of established hypertension occurs and the potassium level is <3.5 mEq/L in the absence of other causes such as new diuretic therapy, it suggests a orteronel-related mineralocorticoid syndrome. A plasma renin activity that is undetectable or low also suggests such a syndrome rather than a secondary cause. While addressing either underlying factors or compliance with current antihypertensives, dosing of orteronel should be followed as outlined in Table 7.

Table 7 Criteria and Appropriate Actions for Hypertension

CTCAE Grade	Event Definition	Action Required
1	Pre-hypertension (systolic BP 120 to 139 mmHg or diastolic BP 80 to 89 mmHg)	No dose modification needed; increase the frequency of BP monitoring as necessary
2	Stage 1 hypertension (systolic BP 140 to 159 mmHg or diastolic BP 90 to 99 mmHg); medical intervention indicated; recurrent or persistent (≥24 hrs); symptomatic increase by >20 mmHg (diastolic) or to >140/90 mmHg if previously within normal limits (WNL); monotherapy indicated.	Concomitant anti-hypertensive agents may initially be administered without dose reduction. If Grade 2 hypertension persists, dose reduction should follow guidelines in Section 6.1.1.2. Supportive care regimen should follow local standard of care
3	Stage 2 hypertension (systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg); medical intervention indicated; more than 1 drug or more intensive therapy than previously used indicated	Interrupt orteronel treatment and follow the guidelines in Section 6.1.1.1. Supportive care regimen should follow local standard of care
4	Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Discontinue orteronel Supportive care regimen should follow local standard of care

Source: CTCAE Version 4.0

Abbreviations: BP = blood pressure; WNL = within normal limits

6.1.3.5. Possible or Suspected Adrenal Insufficiency

If patients experience adrenal insufficiency, the adrenal insufficiency will have the more nonspecific manifestations of glucocorticoid insufficiency, rather than the more specific electrolyte abnormalities of mineralocorticoid insufficiency. Patients experiencing severe physiological stress (eg, surgery, severe infection) should be carefully monitored for adrenal insufficiency. Concomitant medications may complicate the picture of adrenal insufficiency, in particular in patients who are on beta-blockers or diuretics. Concomitant illness such as infection might similarly trigger or worsen symptoms of otherwise mild adrenal insufficiency.

Grading of adrenal insufficiency, the clinical manifestations associated with the specific grade, and management and dosing modifications of orteronel are provided in Table 8. In all cases, actions should include a thorough review for other possible causes or contributors to the presenting symptoms (eg, infection, anemia, or newly introduced concomitant medications).

Table 8 Criteria and Appropriate Actions for Adrenal Insufficiency

Severity	Symptoms/Signs	Action Required/Study Drug Modifications
Possible mild insufficiency	Chronic Grade 1 or Grade 2 fatigue, anorexia <5% weight loss BP normal, possible mild orthostatic hypotension Weight loss	Review medications, check electrolytes, cortisol, and ACTH concentrations Continue study drug as per protocol
Possible or probable moderate adrenal insufficiency, acute or chronic	Grade 2 or 3 fatigue, anorexia, intermittent nausea and vomiting, orthostatic lightheadedness, or weakness Weight loss Definite orthostatic hypotension or below baseline supine BP Possible hyponatremia	Interrupt dosing of orteronel Review medications, check electrolytes, cortisol, and ACTH concentrations Review medications and new diuretic use Dose reduction follows Grade 3 guidelines in Section 6.1.1.1. Discuss with Medical Monitor before restarting orteronel
Possible or probable severe chronic or acute adrenal insufficiency	Grade 3 fatigue, definite anorexia, nausea and vomiting, Severe orthostatic symptoms Prostration Nausea and/or vomiting Hypotension at rest and unable to stand due to orthostatic hypotension, possible hyponatremia	Interrupt dosing of orteronel Manage in an acute care facility Administer IV hydrocortisone and electrolyte/volume replacement Review medications, check electrolytes, cortisol, and ACTH concentrations Dose reduction follows Grade 3 guidelines (Section 6.1.1.1) if a reversible precipitating cause can be identified and reversed. Discuss with Medical Monitor before restarting orteronel Discontinue orteronel permanently if a reversible precipitating cause cannot be identified and reversed or in the event of Grade 4 toxicity

Sources: Arlt and Allolio, 2003, Fauci, 2008, and Salvatori, 2005

Abbreviations: ACTH = adrenocorticotropic hormone; BP = blood pressure; IV = intravenous.

6.1.3.6. Rash (Acneiform or Maculopapular, Localized or Generalized)

Acneiform rash is defined as a disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest, and back. Maculopapular rash is defined as a disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous AEs.

Other types of dermatitis may occur during study treatment; some may require dose modification and supportive care.

Orteronel should be immediately discontinued in a patient experiencing Grade 3 or 4 Stevens-Johnson Syndrome.

Table 9 presents the CTCAE Criteria (Version 4.0) for rash and the appropriate actions to be followed.

Table 9 CTCAE Criteria and Appropriate Actions for Rash (Acneiform or Maculo-papular, Localized or Generalized)

CTCAE Grade	AE	Event Definition	Action Required
1	Acneiform Rash	Papules and/or pustules covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	No dose reduction is necessary. Topical steroids and/or antibiotics as necessary. Reassess after 2 weeks.
	Maculo-papular Rash	Macules/papules covering < 10% body surface area (BSA) with or without symptoms (eg, pruritus, burning, tightness)	No dose reduction is necessary. Topical steroids and/or antibiotics as necessary. Reassess after 2 weeks.
2	Acneiform Rash	Papules and/or pustules covering 10% to 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Follow guidelines for intolerable Grade 2 toxicity (Section 6.1.1.2). Topical steroids and/or antibiotics as necessary. Other types of systemic treatment such as antihistamine may be required. Repeat incidence of Grade 2 skin rash may require prophylactic antihistamine treatment.
	Maculo-papular Rash	Macules/papules covering 10% to 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL	Follow guidelines for intolerable Grade 2 toxicity (Section 6.1.1.2). Topical steroids and/or antibiotics as necessary. Other types of systemic treatment such as antihistamine may be required. Repeat incidence of Grade 2 skin rash may require prophylactic antihistamine treatment.

CTCAE Grade	AE	Event Definition	Action Required
3	Acneiform Rash	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local super-infection with oral antibiotics indicated	Follow guidelines for Grade 3 toxicities in Section 6.1.1.1. Systemic treatment may be considered, including the use of short-term oral steroid (eg, prednisone up to 20 mg), tapering over 7 to 10 days. Monitor signs of GI AEs when prednisone dose is increased. Before adding another oral steroid, consider other options including a combination of topical and oral treatment.
3	Maculo-papular Rash	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	Follow guidelines for Grade 3 toxicities in Section 6.1.1.1. Systemic treatment may be considered, including the use of short-term oral steroid (eg, prednisone up to 20 mg), tapering over 7 to 10 days. Monitor signs of GI toxicity when prednisone dose is increased. Before adding an oral steroid, consider other options including a combination of topical and oral treatment.
4	Acneiform Rash	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive super-infection with IV antibiotics indicated life-threatening consequences	Discontinue orteronel.
	Maculo-papular Rash	Not applicable	

Source: CTCAE Version 4.0
Abbreviations: ADL = activities of daily living; BSA = body surface area; GI = gastrointestinal; IV = intravenous

6.1.3.7. Renal Disorders

The toxicity grade of acute renal injury will be assessed based on the serum creatinine level. Other clinical signs and symptoms, including proteinuria and hematuria, as detected by qualitative or quantitative laboratory tests, may be monitored in addition to creatinine value.

Table 10 presents the appropriate actions to be followed in the event of increased creatinine.

Table 10 Orteronel Treatment Modification for Acute Renal Disorder

CTCAE Grade	Event Definition	Action Required
1	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 to 2 times above baseline	Evaluate patient for urinary tract infection, volume depletion or sub (acute) obstruction. If creatinine remains ≤2 times above baseline, no dose adjustment is required.
2	Creatinine >2 to 3 times above baseline	Evaluate patient for urinary tract infection, volume depletion or sub(acute) obstruction. Hold study drug for 2 weeks. Resume at reduced dose level (200 mg BID) once creatinine is ≤2 times baseline. If the event recurs, discontinue orteronel.
3	Creatinine >3 times baseline or >4.0 mg/dL; hospitalization indicated	Hold study drug until the patient is discharged from the hospital and creatinine level has recovered to <2 times baseline. Follow guidelines for Grade 3 toxicities in Section 6.1.1.1.
4	Life-threatening consequences; dialysis indicated	Discontinue orteronel permanently.

Source: CTCAE Version 4.0

6.1.3.8. Abnormal Liver Function Tests

The incidence of liver function abnormalities is expected to be low. Grade 2 or 3 abnormal liver function tests (LFTs) that are considered by the investigator to be possibly related to orteronel administration should be managed as appropriate, using Table 11 as a guide. A decision to re-challenge and/or resume dosing at a lower dose should be reviewed with the Monitor in all cases.

Table 11 Management of Abnormal AST and ALT Bearing a ≥ Possible Relationship to Orteronel Treatment

AST and/or ALT Elevation Grade (per NCI CTCAE)	Concurrent Bilirubin Level	Required Orteronel Dose Modification
Grade 1	≥1.5 × ULN	Hold until bilirubin resolves to <1.5 X ULN Reduce dose to 200 mg BID, if receiving 300 mg BID, otherwise discontinue orteronel
Grade 2	<1.5 × ULN	Hold until ALT/AST resolve to Grade 1 Reduce dose to 200 mg BID, if receiving 300 mg BID, otherwise discontinue orteronel
Grade 2	≥1.5 × ULN	Discontinue orteronel
Grade 3/4	Any	Discontinue orteronel

Note: Following orteronel dose de-escalation due to AST/ALT and/or bilirubin abnormalities, no re-escalation is permitted.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ULN = upper limit of normal

7. STUDY ASSESSMENTS AND TREATMENT

7.1. Overview

All patients should visit the study center on the days specified within this protocol. The complete schedule of assessments is presented in Appendix E.

7.2. Pre-Screening

Patients must sign a pre-screening ICF and provide an archived tumor sample from a primary biopsy or metastatic lesion for centralized testing of AR expression. Those with AR expression ≥10% are eligible for entry into the main study. Patients may enroll based on local laboratory AR assessment, but will need to submit tissue for confirmation at the central laboratory.

7.3. Full Screening

Consent for the main study must be obtained ≤28 days prior to the initiation of study treatment. The baseline assessments described in Appendix E will be collected prior to the initiation of treatment. Baseline ECHO/MUGA should be within 28 days of treatment.

The physical examination, ECOG performance status, serum/urine pregnancy test (for women of child-bearing potential only), and complete blood counts (CBCs) should be done ≤7 days prior to initiation of treatment. All other assessments should be performed ≤4 weeks prior to initiation of treatment.

- Signed informed consent prior to any other study-related procedures
- Medical history (including assessment of baseline signs and symptoms)

- Physical examination including measurements of height, weight, and vital signs (resting heart rate, blood pressure, respiratory rate, and oral temperature)
- Eastern Cooperative Oncology Group Performance Status (ECOG) performance status (Appendix A)
- Concomitant medication review at the time of informed consent
- Complete blood count (CBC) including 3-part differential and platelets) (may be done up to 72 hours prior to treatment)
- Comprehensive metabolic profile (CMP) (Section 7.6.3) (may be done up to 72 hours prior to treatment)
- Fasting plasma glucose, insulin, c-peptide, and HbA_{1c} (only in patients with a history of diabetes)
- Serum amylase, lipase
- Serum hormone levels: estradiol, total and free testosterone, SHBG, ACTH, DHEA-S, and cortisol
- Serum/urine pregnancy test (for women of childbearing potential only). If done within 72 hours prior to treatment, this test need not be repeated on Cycle 1 Day 1.
- 12-lead ECG
- ECHO/MUGA
- Urinalysis
- CT scan of the chest/abdomen/pelvis
- Bone scan, if clinically indicated
- CT/MRI of the brain, if clinically indicated

7.4. Treatment Assessments

Study treatment will be given in 4-week (28-day) cycles (±5 days) for all patients.

7.4.1. Day 1 of Each Cycle

The following assessments will be performed on Day 1 of each cycle:

- Medical history
- Physical examination including measurements of weight and vital signs (resting heart rate, blood pressure, respiratory rate, and oral temperature) (**weekly during Cycle 1 for Lead-in patients**)
- ECOG performance status
- AE assessment (**weekly during Cycle 1 for Lead-in patients**)
- Concomitant medication review (**weekly during Cycle 1 for Lead-in patients**)
- CBC, including 3-part differential and platelets (Day 1 of each cycle ±3 days) (**weekly during Cycle 1 for Lead-in patients**)(need not be done on Cycle 1 Day 1 if baseline was taken within 72 hours of that day)

- CMP (Day 1 of each cycle ±3 days) (**weekly during Cycle 1 for Lead-in patients**)(need not be done on Cycle 1 Day 1 if baseline was taken within 72 hours of that day)
- Serum hormone levels: estradiol, total and free testosterone, SHBG, ACTH, DHEA-S, and cortisol (**Day 1 of Cycles 2, 4 and End of Treatment only** [see Section 7.5])
- Serum amylase/lipase
- Serum/urine pregnancy test (for women of childbearing potential only). If the baseline reading was done within 72 hours of Cycle 1 Day 1, this test need not be repeated on that day.
- Study drug compliance assessment

7.4.2. Day 1 of Cycle 3 and Every Other Cycle Following (Cycles 5, 7, 9, etc), except where noted

- Fasting plasma glucose, insulin, c-peptide, and HbA_{1c} (only in patients with a history of diabetes)
- 12-lead ECG
- CT scan of the chest /abdomen/pelvis (only those scans abnormal at baseline need to be repeated)
- Bone scan (if clinically indicated)
- CT/MRI of the brain (if clinically indicated)

7.5. End of Study Treatment

Patients are permitted to continue treatment with orteronel until disease progression, or the patient is discontinued due to unacceptable toxicity or a decision to discontinue treatment by the patient or the study physician. Patients will return to the study center ≤30 days after treatment ends for the following assessments:

- Update of medical history
- Physical examination including measurement of weight and vital signs
- ECOG performance status
- AE assessment
- Concomitant medication review
- Study drug compliance assessment
- CBC, including 3-part differential and platelets
- CMP
- Fasting plasma glucose, insulin, c-peptide, and HbA_{1c} (only in patients with a history of diabetes)
- Serum hormone levels: estradiol, total and free testosterone, SHBG, ACTH, DHEA-S, and cortisol

- Serum amylase/lipase
- Urinalysis
- CT scan of the chest /abdomen/pelvis, if no documented progressive disease and the last assessment was >8 weeks prior (only those scans abnormal at baseline need to be repeated)

If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no study treatment is administered, that visit may fulfill the End-of-Treatment Visit.

After withdrawal from protocol treatment, patients must be followed for AEs for 30 calendar days after the last dose of study drug.

7.6. Follow-Up

7.6.1. Follow-Up After Discontinuing Study Treatment

Patients discontinuing treatment for any reason other than progressive disease will be monitored for evidence of disease progression. Disease progression will be assessed every 6 months for 2 years and annually thereafter, up to a maximum of 5 years after the last patient has enrolled on the study. Imaging scans will be done as clinically indicated for evaluation of any new symptoms and assessment for disease progression. After disease progression is documented, patients will be followed as specified in Section 7.6.2.

7.6.2. Follow-Up After Disease Progression

After disease progression is documented, survival will be monitored every 6 months for 2 years and annually thereafter, up to a maximum of 5 years after the last patient has enrolled on the study. Patients may be contacted during outpatient visits or by telephone.

7.6.3. Comprehensive Metabolic Profile

The following laboratory tests should be performed for each patient for assessment of CMP:

- glucose
- blood urea nitrogen (BUN)
- creatinine
- sodium
- potassium
- chloride
- calcium
- carbon dioxide (CO_2)
- alkaline phosphatase (ALP)
- AST
- ALT
- total bilirubin
- total protein

- albumin

8. DRUG FORMATULATION, AVAILABILITY, ADMINISTRATION AND TOXICITY INFORMATION

8.1. Orteronel

Investigational Product	Dosage Form and Strength	Manufacturer
Orteronel	100 mg tablets	Takeda Pharmaceutical Company, Ltd

Orteronel (chemical name, 6-[(7S)-7-hydroxy-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-7-yl]-N-methyl-2-naphthamide) is manufactured by Takeda Pharmaceutical Company, Ltd, Osaka, Japan.

Additional information can be found in the IB.

8.1.1. Labeling, Packaging, and Supply

Orteronel will be packaged in a round, white, high-density polyethylene (HDPE) bottles with a child-resistant cap and induction seal. Each bottle of active orteronel will be labeled with either a single-panel or multi-language booklet label containing pertinent study information, country-specific requirements, and a caution statement.

Orteronel will be supplied as pale red film-coated tablets. Each bottle will contain 64 tablets and each tablet will contain 100 mg of orteronel.

On Day 1 of each cycle, patients will be dispensed sufficient supplies until the next visit.

All study drugs must be kept in a secure place under appropriate storage conditions. Storage conditions for orteronel are included in the IB and on the product label.

8.1.2. Preparation and Administration of Investigational Products

Orteronel 300 mg PO BID continuous daily dosing

Patients will be instructed to take 300 mg orteronel (consisting of three 100-mg tablets at each administration) twice a day with or without food until discontinuation of study treatment/patient withdrawal. The doses of study drug should be taken at the same time each day, approximately 12 hours apart, but not less than 6 hours apart.

Missed doses of study drug may be taken later, provided that the time of dosing is at least 6 hours before the next scheduled dose. Otherwise, patients should resume dosing at the next scheduled time with the prescribed dose. Patients who experience Grade 1 or 2 nausea or vomiting may be advised to take the study drug with or following meals.

On Day 1 of each Cycle, patients will be asked about any missed doses. If a dose is missed, the missed dose will be recorded as "not taken."

8.1.3. Accountability of Investigational Products

The Principal Investigator (or designee) must maintain accountability for all study medication received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if retest date is provided to the investigator
- Frequently verifying that actual inventory matches documented inventory
- Verifying that the drug accountability log is completed for the drug lot used to prepare each dose
- Verifying that all containers used are documented accurately on the log
- Verifying that required fields are completed accurately and legibly

If any dispensing errors or discrepancies are discovered, SCRI Innovations must be notified immediately.

The investigator must maintain a current inventory (drug accountability log) of all study medication delivered to the site, inventory at the site, and patients' use records. This log must accurately reflect the drug accountability of the study medication at all times. The log should include all required information as a separate entry for each patient to whom study medication is dispensed.

The sites should destroy any unused product at the end of the study (or expired product, if any, during the study), per the site's SOPs for doing so. A certificate of destruction that includes a description of the supplies, quantity destroyed, and method of destruction should be returned to the Sponsor.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

9.1. Definitions

Response and progression will be evaluated in this study using the RECIST Version 1.1 (Eisenhauer et al. 2009). Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

9.2. Baseline Eligibility

Measurable Disease:	**Tumor lesions:** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: • 10 mm by CT scan (CT scan slice thickness no greater than 5 mm). • 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable). • 20 mm by chest x-ray. **Skin lesions:** Documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. **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. At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Disease:	All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with >10- to <15-mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses, abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging requirements.
Target Lesions:	The most reproducible 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), should be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and that may be identified as target lesions must meet the criterion or a short axis of >15 mm by CT scan. 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 as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor response.
Non-Target Lesions:	**All other lesions should be identified as non-target lesions at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.**

9.2.1. Guidelines 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, as per protocol screening requirements.

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

Clinical Lesions:	Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). 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:	CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness, contiguously. Spiral CT scan should be performed using a 5-mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
Ultrasound:	When the primary trial endpoint is objective response, ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound may also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
Endoscopy and Laparoscopy:	Use of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Therefore, use of these techniques for objective tumor response should be restricted to validation purposes in specialized centers. Such techniques can be useful in confirming complete pathological response when biopsies are obtained.
Tumor Markers:	Tumor markers alone cannot be used to assess response. If markers are initially above the upper limit of normal, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
Cytology and Histology:	Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

9.2.2. Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions.

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest (nadir) sum since the treatment started, or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.

Evaluation of Non-Target Lesions

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

Stable Disease (SD): Persistence of one or more non-target lesions and/or persistence 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. When the patient also has measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

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). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Confirmation of response (by repeat scans after 4 weeks or as specified in the protocol) is required for trials in which response rate is the primary endpoint, but is not required in randomized trials or trials with primary survival endpoints (i.e., where response is not a primary endpoint).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	NO	CR
CR	SD	NO	PR
CR	NE	NO	PR
PR	SD OR NE	NO	PR
SD	SD OR NE	NO	SD
PD	ANY	YES OR NO	PD
ANY	PD	YES OR NO	PD
ANY	ANY	YES	PD

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of a CR depends upon this determination, it is recommended that the residual lesion be investigated by fine needle aspirate or biopsy to confirm the CR status.

When nodal disease is included in the sum of target lesions, and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression, should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the eCRF.

Non-Measurable Disease Only

When a patient only has non-measurable disease: this circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance; there is no measureable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply non-measureable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

10. STATISTICAL CONSIDERATIONS

10.1. Statistical Design

This is an open-label multicenter study to be conducted in 2 clinical stages. All patients will receive orteronel PO at a dose of 300 mg twice daily (BID).

Lead-in Phase: The first 6 patients treated will be evaluated to confirm the safety and feasibility of this regimen. All 6 patients will be followed weekly for toxicities during the first 4 weeks of treatment. After all 6 patients complete at least 4 weeks of treatment, and if no prohibitive toxicities are identified, continuous study treatment will begin.

Continuous Study Treatment: Patients will continue to be enrolled into their respective cohorts, based on their tumor specificities, to either Cohort 1 (ER-/PR-/HER2-/AR+) or Cohort 2 (ER+ and/or PR+/AR+).

10.2. Analysis Population

The intent-to-treat (ITT) population will consist of all patients enrolled in the trial. Screen failures will not be included in the ITT population.

The Safety population will consist of all patients receiving at least one dose of study drug.

10.3. Sample Size Considerations

Up to 86 patients will be enrolled into this study.

Sample size computations are as follows for each patient cohort.

Cohort 1: For patients with ER-/PR-/HER2-/AR+ tumors, the expected response rate with standard anti-estrogen therapy is expected to be zero. Therefore, a response rate of at least 10% with orteronel therapy would indicate activity and would lead to further investigation. Assuming an evaluable population of 28 patients, the exact 95% confidence interval (CI) for a hypothesized response rate of 11% is (2.4%, 28.6%). In order to incorporate an early stopping rule, Simon's two-stage design is applied using alpha = 0.10 and power = 0.80 with comparison of the hypothesized response rate of 11% versus a conservative estimate of 2%. Initially, 19 patients will be enrolled in this cohort, and if no responses are observed, recruitment to this cohort will stop. Otherwise, enrollment in Cohort 1 will continue to full accrual of 28 evaluable patients. To account for an unevaluable rate of 10%, a total of 31 patients will be enrolled in this cohort.

Cohort 2: For patients with ER+ and/or PR+/AR+ tumors, published data on exemestane as third-line hormonal therapy in postmenopausal women indicate a response rate of 13% and a clinical benefit rate (CR, PR, or SD >24weeks) of 30%. It is hypothesized that treatment with orteronel in this patient population will produce similar results. Assuming an evaluable population of 50 patients, the exact 95% CI for a hypothesized response rate of 14% is (5.8%, 26.7%). In order to incorporate an early stopping rule, Simon's two-stage design is applied using alpha = 0.10 and power = 0.80 with comparison of the hypothesized response rate of 14% versus a conservative estimate of 5.1%. Initially, 26 patients will be enrolled in this cohort, and if one or no responses are observed, recruitment into this cohort will stop. Otherwise, enrollment in

Cohort 2 will continue to full accrual of 50 evaluable patients. To account for an unevaluable rate of 10%, a total of 55 patients will be enrolled in this cohort.

10.4. Planned Interim Analyses

Based on Simon's two-stage design, each cohort individually will undergo an interim analysis for efficacy.

Cohort 1: After enrollment of the first 19 evaluable patients and if no responses are observed, recruitment to this cohort will stop due to lack of efficacy. Otherwise, enrollment will continue to full accrual of 28 evaluable patients. If two or more patients exhibit response at the final analysis, the trial will be considered successful with respect to this patient population.

Cohort 2: After enrollment of the first 26 evaluable patients and if one or no responses are observed, recruitment to this cohort will stop due to lack of efficacy. Otherwise, enrollment will continue to full accrual of 50 evaluable patients. If five or more patients exhibit response at the final analysis, the trial will be considered successful with respect to this patient population.

10.5. Statistical Analyses

All statistical analyses will be performed using SAS 9.1.3 or the current version of SAS available at the time of analysis.

In general, data will be listed and/or summarized and tabulated. Descriptive statistics, such as means, median, standard deviation, minimum and maximum for continuous variables, and counts and percentages for discrete variables, will be used to summarize data as appropriate.

10.6. Efficacy Measures

The primary efficacy endpoints for both Cohort 1 and Cohort 2 are the RR and DCR.

Secondary efficacy endpoints are PFS and OS.

Efficacy analyses will include all patients in the ITT population.

10.6.1. Primary Endpoints

The RR is defined as the percentage of responders (CR+PR) among those patients who are evaluable for response. Response rate will be presented as the point estimate along with 95% confidence intervals calculated using both asymptotic normal approximation and exact binomial methods.

The DCR is defined as the percentage of patients who do not exhibit progression (CR+PR+SD) among those patients who are evaluable for response at 6 months. Disease control rate will be presented as the point estimate along with 95% confidence intervals calculated using both asymptotic normal approximation and exact binomial methods.

10.6.2. Secondary Endpoints

Progression-free survival (PFS) and OS will be analyzed using Kaplan-Meier methods. Each of these endpoints will be presented graphically and further reported using the respective median time point estimate along with its 95% CI.

PFS will be measured from the date of first protocol treatment until the date of objective disease progression or date of death is documented (event), or date of last adequate tumor assessment (censored). If a patient receives non-protocol therapy for the study indication prior to incurring an event, the earliest date of non-protocol treatment recorded will be used (censored). If no post-treatment tumor assessment has been performed, PFS for the patient will be censored at time zero.

OS will be measured from the date of first protocol treatment until the date of death is documented (event), or date last known alive (censored). If a patient receives non-protocol therapy for the study indication prior to incurring an event, the earliest date of non-protocol treatment recorded will be used (censored).

10.7. Safety Review

Treatment-related toxicity is the safety end point.

All patients who received at least one dose of orteronel and who had at least one post baseline safety assessment will be evaluated for toxicity. Patients enrolled, but never treated, will not be included in any of the safety analyses. The actual dose and duration in days of orteronel as well as the dose intensity will be listed and summarized by descriptive statistics. Assessment of safety will be based on the frequency of AEs and on the number of laboratory events that fall outside of predetermined ranges as assessed by the investigator. The incidence of treatment-emergent AEs will be summarized by system organ class, severity (NCI CTCAE, Version 4.0), type of AE, and relationship to study drug. Any other pertinent information collected will be listed, as appropriate.

Observed levels and changes from baseline will be examined for the following hormones at scheduled time point assessments (baseline, at Cycle 2 Day 1, Cycle 3 Day 1, and at the End-of-Treatment Visit): serum estradiol, total and free testosterone, SHBG, ACTH, DHEA-S, and cortisol.

10.8. Biomarkers

Exploratory analysis will be conducted on archived tumor tissue for loss of PTEN and PIK3CA mutations (Section 5.2).

11. SAFETY REPORT AND ANALYSES

11.1. Safety Analyses

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs; measurement of protocol specified hematology, clinical chemistry, and urinalysis variables;

measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) according to the policies of the responsible IRB.

11.2. Adverse Events

11.2.1. Definitions of Adverse Events

An AE is the development of an undesirable medical condition, or the deterioration of a pre-existing medical condition following or during exposure to a medicinal product, whether or not considered causally related to the product.

An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver), or the abnormal results of an investigation (e.g., laboratory findings).

11.2.2. Recording of Adverse Events

All AEs of any patient during the course of the trial will be reported in the case report form, and the investigator will give his or her opinion as to the relationship of the AE to study drug treatment (i.e., whether the event is related or unrelated to study drug administration). If the AE is serious, it should be reported immediately to SCRI Innovations Safety Department. Other untoward events occurring in the framework of a clinical trial are also to be recorded as AEs (i.e., AEs that occur prior to assignment of trial treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

All AEs regardless of seriousness or relationship to orteronel treatment (called trial treatment), spanning from the initiation of trial treatment, until 30 calendar days after discontinuation or completion of protocol-specific treatment as defined by the protocol for that patient, are to be recorded in the eCRF.

11.2.3. Handling of Adverse Events

All AEs resulting in discontinuation from the trial should be followed until resolution or stabilization. Patients must be followed for AEs for 30 calendar days after discontinuation or completion of protocol-specific treatment (e.g., chemotherapy, radiation, oral medications, targeted therapy, and surgery). All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the eCRF. After 30 days of completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

11.3. Serious Adverse Events

11.3.1. Definitions of Serious Adverse Events

The definitions of SAEs are presented in this section. The Principal Investigator is responsible for ensuring that all staff members involved in the study are familiar with the content of this section.

An SAE or reaction is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening (Refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death, if it were more severe.)
- Requires at least a 24-hour in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.)
- Is a congenital anomaly/birth defect
- Is a medically important event.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "in-patient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study), does not require reporting as a SAE to the SCRI Innovations Safety Department.

11.3.2. Serious Adverse Event Reporting by Investigators

It is important to distinguish between "serious" and "severe" AEs, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the eCRF and SAEs on the SAE Report Form.

Adverse events classified by the treating investigator as **serious** require expeditious handling and reporting to SCRI Innovations in order to comply with regulatory requirements. Serious AEs occurring during the course of the study (spanning from the initiation of orteronel treatment through 30 days following the last dose of study medication) will be reported by the Investigator to SCRI Innovations Safety Department via fax or email, and are to be recorded in the eCRF. If a patient experiences an SAE after signing the informed consent, but prior to receiving study drug, the event does not need to be recorded as an SAE unless the investigator feels the event may have been caused by a protocol procedure. The SCRI Innovations Safety Department must be notified of all SAEs, regardless of causality, within 1 business day of the first knowledge of the event by the treating physician or research personnel.

To report an SAE, the SAE Report Form should be completed with the necessary information. All SAEs occurring from the signing of consent until 30 calendar days of last study treatment must be reported to the Sponsor as SAEs on the SAE Report and followed until resolution (with autopsy report if applicable).

Deaths and other SAEs occurring >30 calendar days after last study treatment that are deemed 'possibly' or 'probably' related to orteronel must be reported as SAEs on the SAE Report within 1 business day of first knowledge of the event by the treating physician or research personnel (with an autopsy report if available).

Deaths occurring >30 calendar days after last study treatment and not attributed to study treatment (e.g., disease progression) need not be reported as SAEs, but simply captured on the appropriate eCRF.

The SAE report should be sent to the SCRI Innovations Safety Department via fax or e-mail using the contact information listed below:

SCRI Innovations Safety Department

Fax #: 866-807-4325

Safety Dept. Email: CANN.SAE@scresearch.net

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to SCRI Innovations Safety Department as soon as it is available; these reports

should be submitted using the SCRI Innovations SAE Report Form. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the study reference manual.

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) according to the policies of the responsible IRB.

11.3.3. Sponsor SAE Reporting Requirements

SCRI Development Innovations, LLC will forward SAE and pregnancy information to Millennium Pharmacovigilance within 1 business day of SCRI Innovations Safety Department personnel becoming aware of the SAE.

Millennium Pharmacovigilance
SAE and Pregnancy Reporting Contact Information:
North America PPD, Inc.
Safety and Medical Management, US
Fax: +1 888-488-9697
Hotline number (available 24/7): 1-800-201-8725

The Sponsor (SCRI Development Innovations, LLC) is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, and/or local regulatory requirements.

11.4. Recording of Adverse Events and Serious Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the SAE Report Forms and AE eCRF. Avoid colloquialisms and abbreviations.

All AEs, including those that meet SAE reporting criteria, should be recorded on the AE eCRF; AEs that meet the definition of an SAE should additionally be reported following the procedures noted in Section 11.3.2.

11.4.1. Diagnosis versus Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Principal Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

11.4.2. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the

AE eCRF. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF.

11.4.3. Abnormal Laboratory Values

Any Grade 3 or 4 laboratory abnormalities or any clinically significant Grade 1 or 2 hematology or biochemistry laboratory value(s) should be recorded as an AE. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF.

11.4.4. Deaths

For this protocol, observation of the clinical and laboratory AEs produced by orteronel is the primary efficacy endpoint.

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of disease will be recorded on the "Study Discontinuation" eCRF. All other on-study deaths, regardless of attribution, will be recorded on an SAE Report and expeditiously reported to the SCRI Innovations Safety Department.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE report and Adverse Event page of the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the eCRF Adverse Event page.

11.4.5. Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE (see Section 11.3.2).

11.4.6. Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History eCRF. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an SAE Report Form and/or AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.4.7. Pregnancy, Abortion, or Birth Defects/Congenital Anomalies

Pregnancy, abortion, birth defects, and congenital anomalies are events of special interest. Please refer to Section 11.5 for specific instructions.

11.4.8. New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 11.3). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

11.4.9. Lack of Efficacy

When there is deterioration in the condition for which the study treatment is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or reporting physician considers the study treatment contributed to the deterioration of the condition, the deterioration should be considered lack of efficacy and not an AE.

11.5. Protocol-Defined Events of Special Interest

The following are events of special interest, and will need to be reported expeditiously (see Section 11.3.1):

Pregnancy, Abortion, Birth Defects/Congenital Anomalies:

If a patient becomes pregnant while enrolled in the study, a Pregnancy Form (a paper report form) should be completed and faxed to SCRI Innovations Safety Department. SCRI Innovations Safety Department should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to SCRI Innovations Safety Department.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to the SCRI Innovations Safety Department immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

Any of these events will be reported to Millennium Pharmacovigilance as presented in Section 11.3.3

Orteronel Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the SCRI Innovations Safety Department immediately (within one day) using the corresponding screens in the eCRF, and following the same process described for SAE reporting (see Section 11.3.2) if the overdose is symptomatic.

An overdose is defined as a dose of orteronel administered to a patient that is greater than the protocol-defined dose for the patient. There is no experience with clinically significant

overdosage of orteronel. In the event of drug overdose, the patient should be treated symptomatically, as appropriate. Patients with possible manifestations of adrenal insufficiency may be treated acutely with parenteral or oral glucocorticoids as required and/or tolerated.

11.6. Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints,
call MedComm Solutions at
877-674-3784 (877 MPI DRUG)
(US and International)

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to the SCRI Innovations Safety Department (refer to Section 11.3.2).

12. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This study will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

12.1. IRB Approval

The study protocol, ICF, IB, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., PI payments) and compensation available to the patients and documentation evidencing the PI's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the study start.

The PI/Sponsor/CRO and/or designee will follow all necessary regulations to ensure appropriate, initial, and ongoing, IRB study review. The PI/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates for orteronel will be prepared by Millennium or its representative as required, for submission to the relevant IRB.

12.2. Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendment to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

12.3. Insurance and Indemnity

Details of insurance and/or indemnity will be contained within the written agreement between the PI or site and the Sponsor.

12.4. Informed Consent

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

The informed consent form will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the study. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate understands the implications of participating in this study, the candidate will be asked to give consent to participate in the study by signing an informed consent form. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the informed consent form, to include the patient's signature, will be provided by the investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study should be obtained.

12.5. Confidentiality

12.5.1. Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and national data protection laws, as applicable. HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization from the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this study;
- Who will have access to that information and why;
- Who will use or disclose that information;

- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws;
- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study;
- Whether the authorization contains an expiration date; and
- The rights of a research patient to revoke his or her authorization.

In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorised representatives of Sponsor, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number and initials will identify patients on the eCRF or other documents submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF or database. No material bearing a patient's name will be kept on file by Sponsor. Patients will be informed of their rights within the ICF.

12.5.2. Investigator and Staff Information

Personal data of the investigators and sub-investigators may be included in the SCRI Innovations database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub-investigator, SCRI Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

12.6. Financial Information

The finances for this study will be subject to a separate written agreement between the Sponsor and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

13. RECORD RETENTION AND DOCUMENTATION OF THE STUDY

13.1. Amendments to the Protocol

Amendments to the protocol shall be planned, documented and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor. All amendments require review and approval of all pharmaceutical companies and the Principal Investigator supporting the study. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB at the investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, subject number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB at the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by SCRI Innovations as applicable, after IRB approval and specifically when an increase to dosing or patient exposure and/or subject number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment with IRB and/or FDA approval include, but are not limited to, the following:

- Change to study design
- Risk to patient
- Increase to dose or patient exposure to drug
- Subject number increase
- Addition or removal of tests and / or procedures
- Addition/removal of a new Investigator

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the patients, their consent to continue participation in the study should be obtained.

13.2. Documentation Required to Initiate Study

Before the study may begin, certain documentation required by FDA regulations must be provided by the Investigator. The required documentation should be submitted to:

SCRI Innovations
Attn: Regulatory Affairs
3322 West End Avenue, Suite 900
Nashville, Tennessee 37203
Regulatory Questions: 1-877-MY-1-SCRI

Documents at a minimum required to begin a study in the US include, but are not limited to, the following:

- A signature-authorized protocol and contract;
- A copy of the official IRB approval of the study and the IRB members list;
- Current Curricula Vita for the principal investigator and any associate investigator(s) who will be involved in the study;

- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory;
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed;
- A copy of the IRB-approved consent form containing permission for audit by representatives of SCRI Innovations, Novartis, the IRB, and the FDA;
- Financial disclosure forms for all investigators listed on Form FDA 1572;
- Site qualification reports, where applicable;
- Verification of Principal Investigator acceptability from local and/or national debarment list(s).

13.3. Study Documentation and Storage

The Principal Investigator (PI) must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorised to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patient's eCRF are to be supported by source documentation.

Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the patient's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The PI and each study staff member is responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or investigator study file [ISF]) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed eCRFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain PI name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not

been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

The Investigator shall maintain adequate records of drug disposition, case histories and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., eCRFs and medical records), all original, signed informed consent forms, and copies of all eCRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). SCRI Innovations will notify the investigator(s)/institutions(s) when the study-related records are no longer required.

If the investigator relocates, retires, or for any reason withdraws from the study, both SCRI Innovations and its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met.

13.4. Data Collection

The electronic CRF is the primary data collection instrument for the study. Case report forms will be completed using the English language and should be kept current to enable the Sponsor to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, initials and date of birth will identify the patient in the CRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to SCRI Innovations and replaced instead with the patient number and patient's initials. The investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested on the eCRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown". For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The investigator will electronically sign and date the patient eCRF casebook indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the PI, once all data for that patient is final.

13.5. Study Monitoring, Auditing, and Inspecting

The investigator will permit study-related monitoring, quality audits, and inspections by the Sponsor or its representative(s), government regulatory authorities, and the IRB of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for inspections of applicable study-related facilities. The investigator will ensure that the study monitor or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

At the Sponsor's discretion Source Document Verification may be performed on all data items or a percentage thereof.

Participation as an investigator in this study implies the acceptance of potential inspection by government regulatory authorities, the Sponsor or its representative(s).

13.6. Quality Assurance and Quality Control

Each study site shall be required to have Standard Operating Procedures (SOP's) to define and ensure quality assurance/control processes for study conduct, data generation & collection, recording of data/documentation and reporting according to the protocol, GCP and any applicable local, national or international regulations.

13.7. Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication strategy.

Inclusion of the investigator in the authorship of any multicenter publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the study. The investigator acknowledges that the study is part of a multicenter study and agrees that any publication by the investigator of the results of the study conducted at research site shall not be made before the first multicenter publication. In the event there is no multicenter publication within fifteen (15) months after the study has been completed or terminated at all study sites, and all data has been received, the investigator shall have the right to publish its results from the study, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. Investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the study for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the investigator shall withhold any publication or presentation an additional

sixty (60) days solely to permit the Sponsor to seek patent protection and to remove any SCRI Innovations Confidential Information from all publications.

REFERENCES

Arlt and Allolio, 2003

Arlt W, Allolio B. Adrenal insufficiency. Lancet 2003;361(9372):1881-93.

Basu et al. 2011

Basu B, Ang JE, Crawley D, et al. Phase I study of Abiraterone Acetate in patients with estrogen receptor or androgen receptor postive advanced breast carcinoma resistant to standard endocrine therapies. J. Clin. Oncol. 2011. 29 (suppl; abstract 2525)

Birrell et al. 1998

Birrell SN, Hall RE, and Tilley WD. Role of the Androgen Receptor in Human Breast Cancer. J of Mammary Gland Biology and Neoplasia, 1998. 3(1):95-103.

Carver et al. 2011

Carver B, Chapinski C, Wongvipat J, Hieronymus H, Chen Y, et al. Reciprocal Feedback Regulation of PI3K and Androgen Receptor Signaling in PTEN-Deficient Prostate Cancer. Cancer Cell. 2011;19(5):575-86.

Eisenhauer et al. 2009

Eisenhauer E.A., et al. New response evaluation criteria in solid tumours; revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45 p. 228-47.

Engelman, 2009

Engelman JA. Targeting PI3K signaling in cancer: opportunities, challenges and limitations. Nat Rev Cancer. 2009;9:550–62.

Fauci, 2008

Fauci A, Kasper D, Longo D, Braunwald E, Hauser S, Jameson J, et al. Harrison's Principles of Internal Medicine, 17th Edition. Columbus, OH: McGraw-Hill; 2008.

Gonzalez-Angulo et al. 2009

Gonzalez-Angulo AM, Stemke-Hale K, Pall SL, Carey M, Anarwal, R, et al. Androgen Receptor Levels and Association with PIK3CA Mutations and Prognosis in Breast Cancer. Clin Cancer Res 2009;15:2472-8.

Gucalp and Traina, 2010

Gucalp A and Traina T. Triple-negative Breast Cancer, Role of the Androgen Receptor. The Cancer Journal, 2010. 16(1):62-65.

Gucalp et al. 2012

Gucalp A, Tolaney SM, Isakoff SJ, et al. Targeting the androgen receptor (AR) in women with AR+ ER-/PR- metastatic breast cancer (MBC). J Clin Oncol 30, 2012 (suppl; abstr 1006).

Lehmann et al. 2011

Lehmann, BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011;121(7):2750–67.

Niemeier et al. 2010

Niemeier LA, Dabbs DJ, Beriwal S, Striebel JM, and Bhargava R. Androgen receptor in breast cancer: expression in estrogen receptor-positive tumors and in estrogen receptor-negative tumors with apocrine differentiation. Mod Pathol. 2010;23:205–12.

Salvatori, 2005

Salvatori R. Adrenal insufficiency. JAMA 2005;294(19):2481-8.

Traina et al. 2009

Traina TA, Wolff AC, Giri D, Feigin K, Patil S, Yuan J, et al. Androgen receptor inhibition can stabilize disease in patients with AT+, ER-/PR- metastatic breast cancer. ASCO 2009 Breast Cancer Symposium, Abstract 251.

APPENDICES

Appendix A: ECOG Performance Status Criteria

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix B: Guidelines for Female Subjects of Child-Bearing Potential and Sexually-Active Male Subjects

Women of Child-Bearing Potential are Defined as: any female who has experienced menarche and does not meet the criteria for "Women Not of Childbearing Potential".

Women Not of Childbearing Potential are Defined as:

- Women who are permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
- Women who are >45 years-of-age, not using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (140 pmol/L)
- Women who are >45 years-of-age, using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone-replacement therapy

Acceptable Contraception Methods: Male patients with female partners of child-bearing potential and women patients of childbearing potential are required to use two forms of **acceptable** contraception, including one barrier method, during their participation in the trial and for 4 months following discontinuation of orteronel. Male patients must also refrain from donating sperm for 4 months following discontinuation of orteronel.

The following are acceptable forms of barrier contraception:

- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository

The following are **acceptable** forms of secondary contraception, when used with a barrier method and spermicide:

- True abstinence. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are **not** acceptable methods of contraception
- Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)
- Placement of an intrauterine device (IUD) or intrauterine system, with the exception of IUD progesterone T
- Established use of oral, injected, or implanted hormonal methods of contraception

Unacceptable Contraception Methods: for women of childbearing potential include:

- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Appendix C: New York Heart Association (NYHA) Classifications

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix D: List of QT Prolonging Drugs

Drug	QT risk(*)	Comment
Amiodarone	known risk for TdP	TdP risk regarded as low
Arsenic trioxide	known risk for TdP	
Astemizole	known risk for TdP	CYP3A4 substrate with narrow therapeutic index.
Bepridil	known risk for TdP	
Chloroquine	known risk for TdP	
Chlorpromazine	known risk for TdP	
Cisapride	known risk for TdP	CYP3A substrate with narrow therapeutic index.
Disopyramide	known risk for TdP	
Dofetilide	known risk for TdP	
Domperidone	known risk for TdP	
Droperidol	known risk for TdP	
Halofantrine	known risk for TdP	
Haloperidol	known risk for TdP	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	known risk for TdP	
Levomethadyl	known risk for TdP	Sensitive CYP3A substrate
Mesoridazine	known risk for TdP	
Methadone	known risk for TdP	
Pentamidine	known risk for TdP	
Pimozide	known risk for TdP	Sensitive CYP3A substrate with narrow therapeutic index
Probucol	known risk for TdP	
Procainamide	known risk for TdP	
Quetiapine	possible risk for TdP	Sensitive CYP3A substrate
Quinidine	known risk for TdP	Sensitive CYP3A substrate
Sotalol	known risk for TdP	
Sparfloxacin	known risk for TdP	
Tacrolimus	possible risk for TdP	Sensitive CYP3A substrate with narrow therapeutic index
Terfenadine	Known risk for TdP	Sensitive CYP3A substrate with narrow therapeutic index
Thioridazine	Known risk for TdP	
Vardenafil	possible risk for TdP	Sensitive CYP3A substrate

(*) Classification according to the QTdrugs.org Advisory Board of the Arizona CERT
Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

Appendix D: List of QT Prolonging Drugs (continued)

Drug	QT risk
Alfuzosin	possible risk for Torsades de Pointes
Amantadine	possible risk for Torsades de Pointes
Amitriptyline	conditional risk for Torsades de Pointes
Azithromycin	possible risk for Torsades de Pointes
Chloral hydrate	possible risk for Torsades de Pointes
Citalopram	conditional risk for Torsades de Pointes
Clomipramine	conditional risk for Torsades de Pointes
Clozapine	possible risk for Torsades de Pointes
Desipramine	conditional risk for Torsades de Pointes
Diphenhydramine	conditional risk for Torsades de Pointes
Dolasetron	possible risk for Torsades de Pointes
Doxepin	conditional risk for Torsades de Pointes
Dronedarone	possible risk for Torsades de Pointes
Felbamate	possible risk for Torsades de Pointes
Flecainide	possible risk for Torsades de Pointes
Fluoxetine	conditional risk for Torsades de Pointes
Foscarnet	possible risk for Torsades de Pointes
Fosphenytoin	possible risk for Torsades de Pointes
Galantamine	conditional risk for Torsades de Pointes
Gatifloxacin	possible risk for Torsades de Pointes
Gemifloxacin	possible risk for Torsades de Pointes
Granisetron	possible risk for Torsades de Pointes
Imipramine	conditional risk for Torsades de Pointes
Indapamide	possible risk for Torsades de Pointes
Isradipine	possible risk for Torsades de Pointes
Levofloxacin	possible risk for Torsades de Pointes
Lithium	possible risk for Torsades de Pointes
Mexiletine	conditional risk for Torsades de Pointes
Moexipril/HCTZ	possible risk for Torsades de Pointes
Moxifloxacin	possible risk for Torsades de Pointes
Nicardipine	possible risk for Torsades de Pointes
Nortriptyline	conditional risk for Torsades de Pointes
Octreotide	possible risk for Torsades de Pointes
Ofloxacin	possible risk for Torsades de Pointes
Ondansetron	possible risk for Torsades de Pointes
Oxytocin	possible risk for Torsades de Pointes

Appendix D: List of QT Prolonging Drugs (continued)

Drug	QT risk
Paliperidone	possible risk for Torsades de Pointes
Paroxetine	conditional risk for Torsades de Pointes
Perflutren lipid microspheres	possible risk for Torsades de Pointes
Protriptyline	conditional risk for Torsades de Pointes
Ranolazine	possible risk for Torsades de Pointes
Risperidone	possible risk for Torsades de Pointes
Roxithromycin*	possible risk for Torsades de Pointes
Sertindole	possible risk for Torsades de Pointes
Sertraline	conditional risk for Torsades de Pointes
Solifenacin	conditional risk for Torsades de Pointes
Tizanidine	possible risk for Torsades de Pointes
Trazodone	conditional risk for Torsades de Pointes
Trimethoprim-Sulfa	conditional risk for Torsades de Pointes
Trimipramine	conditional risk for Torsades de Pointes
Venlafaxine	possible risk for Torsades de Pointes
Ziprasidone	possible risk for Torsades de Pointes
(*) Classification according to the QTdrugs.org Advisory Board of the Arizona CERT	

Appendix E: Schedule of Assessments for BRE 203

Procedures	Pre-Treatment		STUDY TREATMENT *Cycle = 28 days*					End of Treatment[n]	Follow Up Prior to Progression[o]	Follow Up After Progression[p]
	Pre-Screening	Full Screening[g]	All Cycles Day 1	Cycle 1 Day 8[l]	Cycle 1 Day 15[l]	Cycle 1 Day 22[l]	Cycle 3 and Every Other Subsequent Cycle (5, 7, 9, etc) Day 1			
Tests and Observations										
Informed Consent		X								
Medical history		X	X					X		
Physical examination, vital signs, height, weight[a]		X	X	X[l]	X[l]	X[l]		X		
ECOG Performance Status		X	X					X		
Adverse event evaluation			X	X[l]	X[l]	X[l]		X	X	
Concomitant medication review		X	X	X[l]	X[l]	X[l]		X		
Survival										X
Study Drug Compliance assessment			X[i]					X		
Dispense Study Drug			X							
Laboratory tests										
CBC, including 3-part differential and platelets[b]		X	X	X[l]	X[l]	X[l]		X		
CMP[c]		X	X	X[l]	X[l]	X[l]		X		
Fasting plasma glucose, insulin, c-peptide, and HbA_{1c} (for diabetic patients only)[d]		X					X	X		
Serum Amylase/lipase		X	X					X		
Serum Hormones: estradiol, total and free testosterone, SHBG, ACTH, DHEA-S, and cortisol		X	X[j]					X		
Pregnancy test (serum/urine)		X	X[k]							
12-lead ECG[e]		X					X			
ECHO/MUGA		X								
Urinalysis		X						X		
Archived tumor tissue[f]	X									
Disease Assessments										
CT scan of the chest, abdomen, pelvis		X					X[m]	X[m]		
Bone scan		X[h]					X[h]			
CT/MRI of the brain		X[h]					X[h]			

Appendix E: Schedule of Assessments for BRE 203 (continued)

[a] Physical examinations will include measurements of vital signs (resting heart rate, blood pressure, respiratory rate, oral temperature). At the baseline visit only, height will also be recorded and weight will be recorded only on Day 1 of each cycle.

[b] Hematological parameters include the following laboratory tests: complete blood count consisting of red blood cell count (RBCs), hemoglobin, total white blood count (WBC) with differential, and platelet count. Do not repeat on C1D1, if baseline within 72 hours.

[c] CMP assessment includes the following laboratory tests: glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO2, alkaline phosphatase (ALP), AST, ALT, total bilirubin, total protein, and albumin. Do not repeat on C1D1, if baseline within 72 hours.

[d] Fasting plasma glucose, insulin, and c-peptide will be drawn at screening, predose on Day 1 of odd-numbered cycles (Cycles 3, 5, 7, etc), and at study completion for patients with a history of diabetes.

[e] A single ECG will be obtained at baseline for QTcF interval assessment for all patients. A single ECG will also be obtained predose on Cycle 3 Day 1 and then every 2nd cycle (Cycles 5, 7, 9, etc).

[f] Archived tumor tissue from a primary biopsy or metastatic lesion is required for centralized testing of AR expression. Patients with AR expression ≥10% will be screened for enrollment into the study. Additional tumor tissue, if available from the patients enrolled on study, will be retained to perform correlative testing (15 to 20, 4 um unstained slides). Patients may enroll based on local laboratory AR assessment, but will need to submit tissue for confirmation at the central laboratory.

[g] Informed consent must be obtained ≤28 days prior to the initiation of trial treatment. The physical examination, ECOG performance status, serum/urine pregnancy test (for women of child-bearing potential only), and complete blood counts (CBCs) should be done ≤7 days prior to initiation of treatment.

[h] If clinically indicated.

[i] Day 1 of each cycle following Cycle 1

[j] Serum hormone levels will be drawn at screening, on Day 1 of Cycles 2 and 4, and at the end of study visit.

[k] Do not repeat on Cycle 1 Day 1, if baseline was done within 72 hours.

[l] Lead-in patients only

[m] If no documented progressive disease and the last assessment was >8 weeks prior. Only abnormal scans at baseline need to be repeated.

[n] All patients will undergo the end-of-treatment assessments listed within 30 days after treatment ends. Patients must be followed for AEs for 30 calendar days after the last dose of study drug.

[o] Patients discontinuing treatment for any reason other than progressive disease will be monitored for evidence of disease progression. Disease progression will be assessed every 6 months for 2 years and annually thereafter, up to a maximum of 5 years after the last patient has enrolled on the study. Imaging scans will be done as clinically indicated for evaluation of any new symptoms and assessment for disease progression.

[p] After disease progression is documented, survival will be monitored every 6 months for 2 years and annually thereafter, up to a maximum of 5 years after the last patient has enrolled on the study. Patients may be contacted during outpatient visits or by telephone.