SCRI BRE 203: A Phase II Study with Orteronel as Monotherapy in Patients with Metastatic Breast Cancer (MBC) that Expresses the Androgen Receptor (AR)

Fast Facts

Orteronel will be supplied to SCRI Innovations by Millennium Pharmaceuticals, Inc.
The planned oral dose of orteronel is 300 mg BID.

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.

Hormone tests are performed at QUEST and are sponsor funded

Inclusion Criteria

1. Voluntary 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

8. Adequate hematological function, defined as:
    - Absolute neutrophil count (ANC) ≥1.25 x 109/L
    - Platelets ≥75 x 109/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 theCockcroft-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 childbearing 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 study and follow-up procedures.

Exclusion Criteria

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 (HbAlc) 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.

Pre-Study Parameters

1. History and physical including vitals, height, weight, ECOG PS, concomitant medication assessment,
2. Labs including CBC, CMP, amylase, lipase
3. Fasting plasma glucose, insulin, c-peptide, and HbA1c (for diabetic patients)
4. Serum Hormones: estradiol, total and free testosterone, SHBG, ACTH, DHEA-S, and cortisol *(tests performed at QUEST and sponsor funded)*
5. Pregnancy test (serum/urine)
6. Urinalysis
7. ECG, ECHO/MUGA
8. CT scan of chest, abdomen, pelvis;
9. Bone Scan (if clinically indicated)
10. CT/MRI of the brain (if clinically indicated)

Schema

Lead-in Phase

(Following Pre-Screening for AR Expression)
N = 6
Orteronel 300 mg PO BID Continuous

Patients will be followed weekly

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After all 6 patients complete at least 4 weeks of treatment, and if no prohibitive toxicities are identified, the study will continue to enroll patients until full enrollment has been achieved
(a total of 86 patients)

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Continuous Study Treatment

(Following Pre-Screening for AR Expression)

Orteronel 300 mg PO BID Continuous

N = 31 (Cohort 1: ER-/PR-/HER2-/AR+)
N = 55 (Cohort 2: ER+ and/or PR+/AR+)

Treatment cycles will be repeated every 4 weeks.
Patients will be evaluated with CT scans every 2 treatment cycles (every 8 weeks). Treatment will continue until disease progression or unacceptable toxicity occurs.