**SHERBOC: A Double-blind, Placebo-controlled, Phase 2 Trial of Seribantumab (MM-121) plus Fulvestrant in Postmenopausal Women with Hormone Receptor-positive, Heregulin Positive, HER2-negative Metastatic Breast Cancer Whose Disease Progressed after Prior Systemic Therapy**

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1. **ErbB3 (HER3) receptor and its ligand heregulin (HRG) in the progression of multiple types of cancer has been established.**
2. **Previous research showed that ~45% of ER/PR positive, HER2 negative metastatic breast cancers (mBC) are HRG positive.**
3. **Seribantumab (MM-121) is a fully human IgG2 antibody developed to block the binding of HRG to ErbB3.**

**Methods**

- A retrospective analysis of three randomized Phase 2 studies adding to standard of care therapies.
- **In a previous Phase 2 study, HRG+ patients with mBC appeared to benefit from**
- **Additionally, blockade of HRG-induced HER3 signaling by seribantumab may counter effects of HRG on cancer cells, with the potential for improved outcomes in HRG+ patients.**

**Key Eligibility Criteria**

- **Postmenopausal adult women with histologically or cytologically confirmed ER+ and/or PR+ (with staining of ≥1% cells) and HER2 negative locally advanced or mBC.**
- **A positive in-situ hybridization (ISH) test for HRG with a score of ≥1+, as determined by centralized testing of unstained tumor tissue.**
- **Progressed following systemic therapy with a CDK inhibitor (e.g. palbociclib).**
- **Patients cannot have received more than two prior lines of therapy in the locally advanced or metastatic disease setting, and cannot have received chemotherapy in the locally advanced or metastatic disease setting.**
- **Must have at least one lesion amenable to fresh tissue biopsy.**
- **Documented progression of locally advanced or metastatic disease during or after the last systemic therapy by RECIST 1.1.**
- **Patients with bone-only disease are eligible if they have at least 2 lytic lesions on CT or MRI.**
- **Recovered from clinically significant effects of any prior surgery, radiotherapy, or other antiangiogenic therapies.**
- **Adequate end-organ function, ECOG performance status of 0 or 1.**

**Primary Objectives**

- To determine whether the combination of seribantumab plus fulvestrant is more effective than placebo plus fulvestrant based on investigator assessed Progression Free Survival (PFS) in HRG positive patients (defined as HRG ISH score of ≥ 1+).
- To determine whether the combination of seribantumab plus fulvestrant is more effective than placebo plus fulvestrant for the following clinical outcome parameters:
  - Time to Progression (TTP)
  - Overall Survival (OS)
  - Objective Response Rate (ORR)
- To describe the safety profile in combination with fulvestrant.
- To characterize the pharmacokinetic (PK) profile of seribantumab when given in combination with fulvestrant and of fulvestrant when given in combination with seribantumab.
- To assess the correlation for HRG expression between fresh tissue biopsies and archival samples where available.

**Study Design**

- Study arm: 1:1 randomization to receive:
  - Arm A: Seribantumab at fixed dose of 3000 mg IV on days 1 and 15 of each 28-day cycle and fulvestrant 500 mg IM on days 1 and 15 of Cycle 1, and on Day 1 of each subsequent 28-day cycle.
  - Arm B: Placebo IV on days 1 and 15 of each 28-day cycle and fulvestrant: 500 mg IM on Day 15 of Cycle 1, and on day 1 of each subsequent 28-day cycle.
- Randomization stratified based on:
  - Bone-only disease (yes, no)
  - Geographic region (US, non-US)
- Treatment until investigator-assessed progressive disease, clinical deterioration, or unacceptable toxicity.
- Disease assessment every 8 weeks from randomization regardless of treatment schedule.
- Tissue collection for biomarker analysis.
- Plasma samples collection for PK, and an ESR1 mutation analysis.

**Projected Sites (85 Total)**

- United States
- Austria
- Belgium
- Canada
- Germany
- Italy
- Spain
- Canada
- Germany
- Italy
- Spain

**Registered Clinical Trials Registry number NCT 03241810**

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