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

Poster # OT3-06-01

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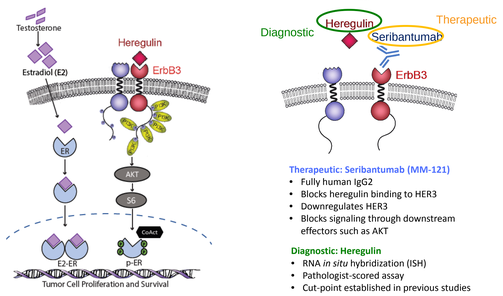
Introduction

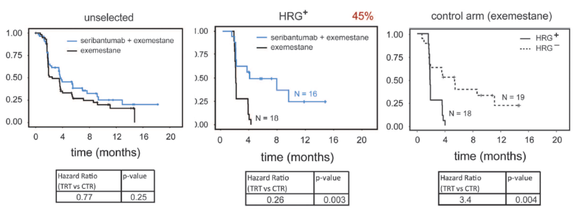
- The role of the ErbB3 (HER3) receptor and its ligand heregulin (HRG) in the progression of multiple types of cancer has been established.
- Previous research showed that ~45% of ER/PR positive, HER2 negative metastatic breast cancers (mBC) are HRG positive.
- Seribantumab (MM-121) is a fully human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



Therapeutic: Seribantumab (MM-121)
- Fully human IgG2
- Blocks heregulin binding to HER3
- Downregulates HER3
- Blocks signaling through downstream effectors such as AKT

Diagnostic: Heregulin
- RNA *in situ* hybridization (ISH)
- Pathologist-scored assay
- Cut-point established in previous studies

- In a previous Phase 2 study, HRG+ patients with mBC appeared to benefit from seribantumab vs. control.



Hazard Ratio (TRT vs CTR)	p-value
0.77	0.25

Hazard Ratio (TRT vs CTR)	p-value
0.26	0.003

Hazard Ratio (TRT vs CTR)	p-value
3.4	0.004

- A retrospective analysis of three randomized Phase 2 studies adding to standard of care (SOC) in ER/PR+ mBC, NSCLC, and platinum resistant/refractory ovarian cancer reported:
  - The presence of tumor cell HRG mRNA was prognostic for shortened PFS with SOC treatment
  - The addition of seribantumab to SOC therapy improved PFS for patients with HRG+ tumors
- These data suggest that HRG expression may define a drug tolerant cancer cell phenotype characterized by poor response to multiple classes of cytotoxic and targeted therapies.
- 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.

Objectives

Primary:

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+)

Secondary:

- To determine whether the combination of seribantumab plus fulvestrant is more effective than placebo plus fulvestrant in HRG+ patients for the following clinical outcome parameters:

  Time to Progression (TTP)
  Overall Survival (OS)
  Objective Response Rate (ORR) based on RECISTv1.1
- To describe the safety profile of seribantumab 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

Exploratory:

- To assess the correlation for HRG expression between fresh tissue biopsies and archival samples where available

Methods

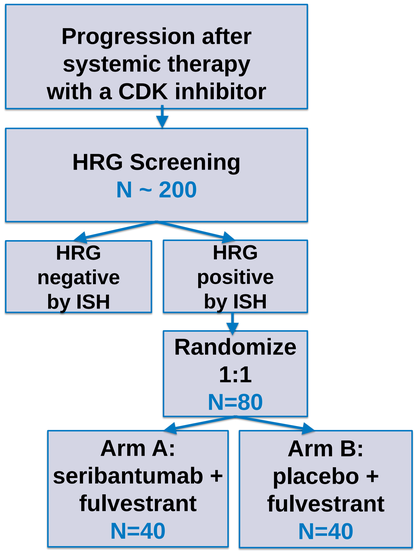
- Randomized, double-blind, placebo-controlled, multi-center Phase 2 study
- Prospective selection of patients with HRG+ disease using a most recent tissue sample
- Approximately 200 patients will be screened to support enrollment of 80 HRG+ patients
- 1:1 randomization to receive:

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 days 1 and 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.

Study Design

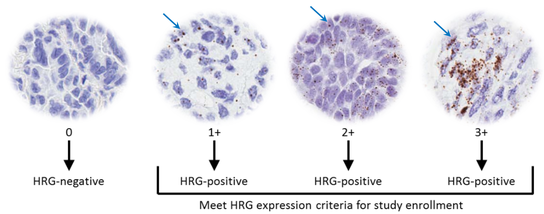


Key Eligibility Criteria

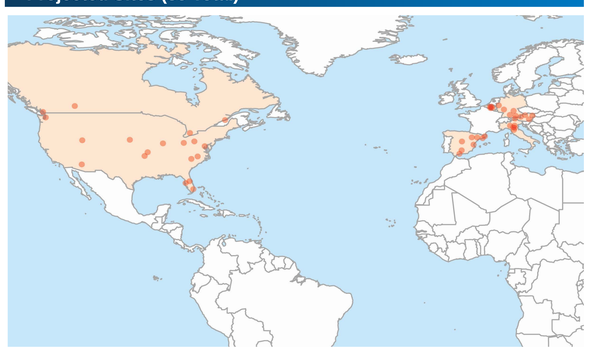
- Postmenopausal adult women with histologically or cytologically confirmed ER+ and/or PR+ (with staining of ≥ 1% cells) and HER2 negative locally advanced or mBC
- A positive in-situ hybridization (ISH) test for HRG with a score of ≥1+, as determined by centralized testing of unstained tumor tissue
- 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 v1.1. 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 antineoplastic therapy
- Adequate end-organ function, ECOG performance status of 0 or 1

Heregulin mRNA Assay

- Assay developed to quantitate HRG mRNA in tumor tissue
  - *In situ* hybridization (ISH) assay technology developed by Advanced Cell Diagnostics
  - HRG-specific assay optimized by Merrimack Pharmaceuticals, Inc.
  - LabCorp CLIA lab performing assay and reporting results within 7 calendar days of sample receipt
  - Companion diagnostic being developed by Leica Biosystems
- Fully automated assay performed on a Leica BOND autostainer
- RNA transcripts visualized as dots and scored by a pathologist using a defined scoring system of 0, 1+, 2+ and 3+
- Acceptable tissue sources include surgical resections, core needle biopsies, fine needle aspirates and pleural effusions
- Integrated QC in the assay testing RNA integrity



Projected Sites (85 Total)



Participating Countries		
United States	Austria	Spain
	Belgium	Italy
	Canada	Germany

A PASSION FOR OUTTHINKING CANCER

Clinical Trials Registry number NCT 03241810
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