SHERLOC: A Phase 2 Study of Seribantumab (MM-121) in Combination with Docetaxel versus Docetaxel Alone in Patients with Heregulin Positive (HRG+), Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Poster # 13960

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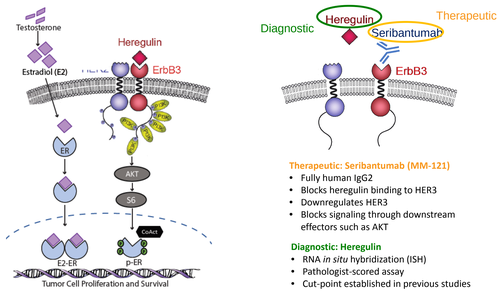
Introduction

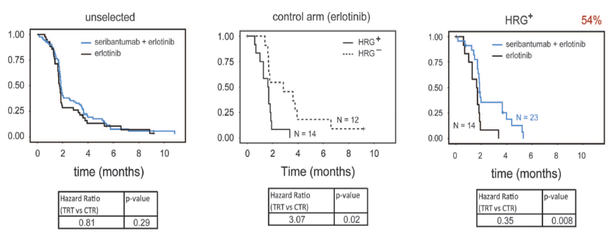
- The role of the ErbB3 (HER3) receptor and its ligand heregulin (HRG) in the progression of multiple types of cancer has been established.
- Previous research showed that ~50% of non-small cell lung cancer (NSCLC) tumors are HRG-positive.
- Seribantumab (MM-121) is a fully human IgG2 antibody developed 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-positive patients with NSCLC appeared to benefit from seribantumab *vs*. control.



Hazard Ratio (TRT vs CTR)	p-value
0.81	0.29

Hazard Ratio (TRT vs CTR)	p-value
3.07	0.02

Hazard Ratio (TRT vs CTR)	p-value
0.35	0.008

- A retrospective analysis of three randomized Phase 2 studies adding to standard of care (SOC) in NSCLC, ER/PR+ mBC, ,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-positive patients.

Objectives

Primary:

- To determine whether the combination of seribantumab plus docetaxel is more effective than docetaxel alone based on investigator assessed Progression-Free Survival (PFS) according to RECIST 1.1 in HRG positive patients (defined as HRG ISH score of ≥1+)

Secondary:

- To determine whether the combination of seribantumab plus docetaxel is more effective than docetaxel alone in HRG-positive patients (defined as HRG ISH score of > 1+) for the following clinical outcome parameters:
  - Overall Survival (OS)
  - Objective Response Rate (ORR) based on RECISTv1.1
  - Time to Progression (TTP)
- To describe the safety profile of seribantumab in combination with docetaxel
- To characterize the pharmacokinetic (PK) profile of seribantumab when given in combination with docetaxel and of docetaxel when given in combination with seribantumab

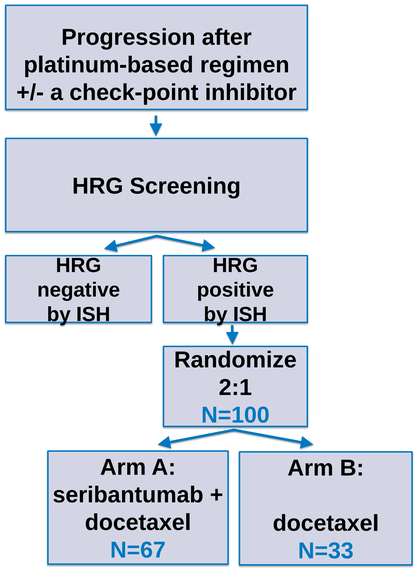
Exploratory:

- To evaluate if mechanistically-linked exploratory biomarkers from tumor tissue or blood samples correlate with clinical outcomes

Methods

- Randomized, open-label, international, multi-center Phase 2 study
- Prospective selection of patients with HRG-positive disease using a most recent tissue sample
- Approximately 100 HRG-positive patients will be enrolled and randomized in a 2:1 ratio to receive seribantumab plus docetaxel (experimental treatment arm), or docetaxel alone (control arm)
- Experimental treatment arm (Arm A): seribantumab: fixed dose of 3000 mg intravenously (IV) on day 1 of each 21-day cycle plus docetaxel: 75 mg/m^2 IV on day 1 of each 21-day cycle
  Control arm (Arm B): docetaxel: 75 mg/m^2 IV on day 1 of each 21-day cycle
- Randomization stratified based on:
  - Number of prior systemic therapies for locally advanced and/or metastatic disease (1, >2)
  - Geographic region (US, Asia, non-US and non-Asia)
- Treatment until investigator-assessed progressive disease or unacceptable toxicity
- Local tumor assessments every 6 weeks evaluated using RECIST v1.1 guidelines
- The study has ≥ 80% power to detect a 3-month improvement in median PFS over 3 months (hazard ratio ≤ 0.50), using a one-sided, stratified log-rank test at a significance level of 0.025

Study Design

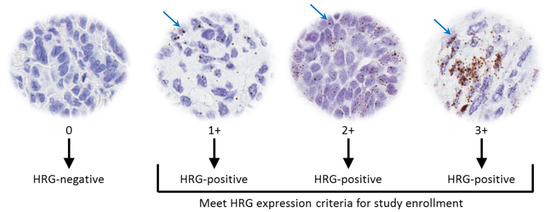


Key Eligibility Criteria

- Patients with locally advanced or metastatic NSCLC histologically classified as adenocarcinoma EGFR wild type with no known ALK rearrangement
- Disease progression following one to two SOC for locally advanced and/or metastatic disease, including platinum-based therapy and, where available and clinically indicated, anti-PD-1/PD-L1 therapy
- Patients who have received docetaxel for treatment of advanced/metastatic disease are not eligible for docetaxel-containing arm
- Must have:
  - Available recent tumor specimen, collected following completion of most recent systemic therapy OR
  - A lesion amenable to either core needle biopsy or fine needle aspiration
- A positive *in situ* hybridization (ISH) test for HRG with a score of >1+, as determined by centralized testing
- ECOG performance status of 0 or 1
- Screening ECG without clinically significant abnormalities
- Age ≥ 18 years

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	Germany	Spain
Australia	Hungary	Taiwan
Canada	Poland	Thailand
France	South Korea	United States

A PASSION FOR OUTTHINKING CANCER

Clinical Trials Registry number NCT 03241810
For more information, please contact Sara Ghassemifar: sghassemifar@merrimack.com

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