Rationale

- The role of the ErbB3 receptor and its ligand heregulin (HRG) in the progression of multiple types of cancer has been well established.
- Seribantumab (MM-121) is a fully human IgG2 antibody developed to block the binding of HRG to ErbB3.

Conceptual Model of HRG Impact on Treatment Outcomes

- In preclinical in vitro and in vivo models, HRG impacts response to targeted therapies and chemotherapies, including docetaxel and pemetrexed, and the addition of seribantumab restores response to these therapies.
- In retrospective analysis of three prior randomized Phase 2 studies, including NSCLC, high levels of HRG mRNA predicted shortened PFS in patients who received standard of care (SOC) therapy, while the addition of seribantumab to SOC improved PFS in patients with HRG+ tumors.
- Approximately half of NSCLCs are HRG positive, defined by mRNA expression measured by an in situ hybridization assay being developed as a companion diagnostic for seribantumab.
- There are no clinically relevant biomarkers to inform treatment options for NSCLC patients post-progression on anti-PD-1 therapies.

Study Design

- HRG screening performed using recently acquired tumor sample:
  - Surgical excisions
  - Core needle biopsies
  - Fine needle aspirates
  - Option to submit archival tissue for HRG pre-screening
  - Approximately 50% HRG+ prevalence observed in NSCLC

Key Eligibility Criteria

- Patients with cytotologically or histologically documented locally advanced or metastatic NSCLC (any histology)
- EGFR wild type, no known ALK rearrangement
- Disease progression or evidence of recurrent disease during or after the last systemic therapy as documented by radiographic assessment
- Prior therapy for locally advanced and/or metastatic disease:
  - Up to 3 prior systemic anti-cancer regimens
  - Must have received docetaxel, pembrolizumab, or other anti-PD-1 or anti-PD-L1 therapy (approved or investigational in any line of treatment)
  - No prior treatment with an anti-ErbB3 antibody
- Clinically eligible for intended chemotherapy, docetaxel or pemetrexed, once every three weeks per the investigator’s judgment
- Patients who have received docetaxel for treatment of advanced/metastatic disease are not eligible for docetaxel-containing arm, and patients who have received pemetrexed for treatment of advanced/metastatic disease are not eligible for pemetrexed-containing arm
- Must have:
  - Available recurrent 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
  - ≥ 18 years of age

Methods

- Randomized, open-label, Phase 2 study
- Prospective selection of patients with HRG+ disease using a recent tissue sample
- Approximately 560 patients will be screened to support enrollment of 280 HRG+ patients
- 2:1 randomization to receive seribantumab plus investigator’s choice of docetaxel or pemetrexed, or docetaxel or pemetrexed alone
- Randomization stratified based on:
  - Chemotherapy backbone (docetaxel, pemetrexed)
  - Number of prior systemic therapies for locally advanced and/or metastatic disease (1-2)
  - Geographic region (US, Asia, non-US and non-Asia)
- Q3W dosing schedule
- Treatment until investigator-assessed progressive disease or unacceptable toxicity
- Local tumor assessments every 6 weeks evaluated using RECIST v1.1 guidelines
- Interim analysis planned when 50% of final OS events have been reported
- Overall survival follow-up

Primary Objective

To determine whether the combination of seribantumab plus docetaxel or seribantumab plus pemetrexed is more effective than docetaxel or pemetrexed alone on Overall Survival in HRG+ patients (defined as HRG ISH score of ≥1+)

Secondary & Exploratory Objectives

Secondary:
- To determine whether the combination of seribantumab plus docetaxel or seribantumab plus pemetrexed is more effective than docetaxel or pemetrexed alone in HRG+ patients (defined as HRG ISH score of ≥1+) for the following clinical outcome parameters:
  - Investigator Assessed - Progression-Free Survival (PFS)
  - Independent Central Review – PFS
  - Objective Response Rate (ORR) based on RECISTv1.1
  - Time to Progression (TTP)
- To describe the safety profile of seribantumab in combination with docetaxel or pemetrexed
- To assess health-related quality of life (HRQoL) in NSCLC
- To characterize the pharmacokinetic (PK) profile of seribantumab when given in combination with docetaxel or pemetrexed and of docetaxel or pemetrexed when given in combination with seribantumab

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

Heregulin mRNA Assay

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

Activity of Seribantumab Plus Docetaxel or Pemetrexed in NSCLC Xenograft Model

The combination of seribantumab with either docetaxel or pemetrexed delays in vivo growth of the H132 NSCLC xenograft model more than any of the agents alone.