

**SHERBOC: A Double-blind, Placebo-controlled, Phase 2 trial of  
Seribantumab Plus Fulvestrant in Postmenopausal Women with  
Hormone Receptor-positive, Heregulin Positive (HRG+), HER2  
Negative Metastatic Breast Cancer Whose Disease Progressed After  
Prior Systemic Therapy**

**Merrimack Pharmaceuticals, Inc.**

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## Abbreviations

Abbreviations	Definitions
ABC	Advanced breast cancer
AE	Adverse event
AESI	Adverse event of special interest
AI	Aromatase inhibitor
AKT	Protein kinase B
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCO	American Society for Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC <sub>t</sub>	Area under the concentration-time curve
BTC	Betacellulin
C <sub>avg</sub>	Average serum concentration
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Clearance
C <sub>max</sub>	Maximum serum concentration
CMH	Cochran-Mantel-Haenszel (test)
C <sub>min</sub>	Minimum serum concentration
CNB	Core needle biopsy
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTG	Cell TiterGlo
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG (PS)	Eastern Cooperative Oncology Group (performance status)
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
ErbB	Epidermal growth factor family of receptor tyrosine kinases
ESR1	Estrogen receptor alpha
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FGF	Fibroblast growth factor
FL-IHC	Fluorescence-based immunohistochemistry
FNA	Fine needle aspiration
g	Gram
GCSF	Granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GnRH	Gonadotropin-releasing hormone

GR	Grade
HAHA	Human anti-human antibodies
HER2	Human epidermal growth factor receptor 2
HGF	Hepatocyte growth factor
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HRG	Heregulin
HR-positive	Hormone receptor positive
IB	Investigator's Brochure
ICH	International conference on harmonization
Ig	Immunogenicity
IGF	Insulin-like growth factor
IGF-1R	Insulin-like growth factor 1 receptor
IHC	Immunohistochemistry
INR	International normalized ratio
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
ISH	In-situ hybridization
ITT	Intent to treat
MITT	Modified Intent to treat
IV	Intravenous
IWRS	Interactive web response system
kg	Kilogram
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LVEF	Left ventricle ejection fraction
mBC	Metastatic breast cancer
mcg	Micrograms
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mOC	Metastatic ovarian cancer
mL	Milliliter
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
MUGA	Multiple gated acquisition scan
NCI	National Cancer Institute
NRG	Neuregulin
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall survival
p.o.	Per os (oral administration)
PD	Progressive disease
PE	Pulmonary embolism
PET-CT	Positron emission tomography - computed tomography
PFS	Progression free survival
PgR	Progesterone receptor
PI3K	Phosphatidylinositol-3-kinase

PK	Pharmacokinetic(s)
PR	Partial response
PTT	Prothrombin time
QD	Every day
Q1W	Every week
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QW	Weekly
RANKL	Receptor activator of nuclear factor kappa-B ligand
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RNAi	Ribonucleic acid interface
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAF	Safety Population
SAP	Statistical Analysis Plan
SD	Stable disease
SERD	Selective estrogen receptor disruptor
SERM	Selective estrogen receptor modifier
SmPC	Summary of Product Characteristics
TCGA	The Cancer Genome Atlas
TKI	Tyrosine kinase inhibitor
T <sub>max</sub>	Time to maximum serum concentration
TTP	Time to Progression
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeial Convention
VD <sub>ss</sub>	Volume of distribution at steady state
WBC	White blood cell



## Study Synopsis

<b>SPONSOR:</b>	Merrimack Pharmaceuticals, Inc. One Kendall Square Building 700, Suite B7201 Cambridge, MA, USA 02139-1670
<b>PROTOCOL TITLE:</b>	A Double-blind, Placebo-controlled, Phase 2 trial of Seribantumab Plus Fulvestrant in Postmenopausal Women with Hormone Receptor-positive, Heregulin Positive (HRG+), HER2 Negative Metastatic Breast Cancer Whose Disease Progressed After Prior Systemic Therapy
<b>TRIAL LOCATION:</b>	North America and Europe
<b>PROTOCOL NUMBER:</b>	MM-121-02-02-10
<b>STUDY OBJECTIVE(S):</b>	<p><b>Primary Objective:</b></p> <ul style="list-style-type: none"> <li>To determine whether the combination of seribantumab + fulvestrant is more effective than placebo + fulvestrant based on investigator assessed Progression Free Survival (PFS) in HRG positive patients (defined as HRG ISH score of <math>\geq 1+</math>)</li> </ul> <p><b>Secondary Objectives:</b></p> <ul style="list-style-type: none"> <li>To determine whether the combination of seribantumab + fulvestrant is more effective than placebo + fulvestrant in HRG positive patients for the following clinical outcome parameters: <ul style="list-style-type: none"> <li>Time to Progression (TTP)</li> <li>Overall Survival (OS)</li> <li>Objective Response Rate (ORR) based on RECISTv1.1</li> </ul> </li> <li>To describe the safety profile of seribantumab in combination with fulvestrant</li> <li>To characterize the pharmacokinetic (PK) profile of seribantumab when given in combination with fulvestrant and of fulvestrant when given in combination with seribantumab</li> </ul> <p><b>Exploratory Objectives:</b></p> <ul style="list-style-type: none"> <li>To assess the correlation for HRG expression between fresh tissue biopsies and archival samples where available</li> </ul>
<b>STUDY DESIGN:</b>	<p>This is a multi-center, randomized, double-blind, placebo-controlled Phase 2 study of seribantumab or placebo with fulvestrant in patients with ER/PR positive, HER2 negative, metastatic, unresectable breast cancer whose tumor expresses HRG as measured by RNA in-situ hybridization (RNA-ISH).</p> <p>Following signing informed consent for biomarker testing and evaluation of initial eligibility criteria, all patients will provide a tissue sample (which meets the requirements for collection and processing as outlined in the study lab manual) to the designated central lab facility for HRG testing. If adequate tissue is not available, patients should undergo a tumor biopsy to acquire the necessary tissue for HRG testing. For these procedures, investigators are asked to choose an easily accessible tumor lesion to minimize any possible risk associated with the collection of the tissue. As a general guideline, if the selected procedural location of the biopsy has an established serious complication rate of <math>&gt;2\%</math> at the institution completing</p>

	<p>the procedure, this is considered a high risk procedure and should be avoided. Upon receipt of a tissue sample at the central lab, the investigational site will be informed of the results within 7 days. Patients with a positive HRG status, defined as HRG ISH score of <math>\geq 1+</math>, will be eligible for randomization.</p> <p>Prior to receiving the first dose, all HRG positive patients that receive HRG results for eligibility based on testing of archived samples will also be asked to undergo a fresh research biopsy, prior to first dose. An additional sample will not be requested from patients who underwent a fresh biopsy for eligibility testing. The sample should be collected and processed according to the laboratory manual.</p> <p>Once all screening procedures have been completed and eligibility for treatment randomization (including HRG positive ISH result) has been determined, the investigator may randomize the patient. Patients will be randomized in a 1:1 ratio (experimental arm versus comparator arm) using an Interactive Web Response System (IWRS). Randomization will be stratified based on bone-only disease (yes, no) and geographic region (US, non-US). Patients will be assigned to Arm A or Arm B:</p> <p><b>Arm A (Experimental Arm):</b> Seribantumab: fixed dose of 3000 mg intravenously (IV) on day 1 and 15 of each 28-day cycle</p> <p>Fulvestrant: 500 mg intramuscularly (IM) on Days 1 and 15 of Cycle 1, and then on Day 1 of each subsequent 28 day cycle</p> <p><b>Arm B (Control Arm):</b> Placebo: intravenously (IV) on day 1 and 15 of each 28-day cycle Fulvestrant: 500 mg intramuscularly (IM) on Days 1 and 15 of Cycle 1, and then on Day 1 of each subsequent 28 day cycle</p> <p>Treatment will start within 7 days following randomization. It is intended that patients will be treated until investigator-assessed disease progression or unacceptable toxicity, whichever comes first. Tumor assessments will be measured and recorded by the local radiologist every 8 weeks (<math>\pm 5</math> days) from randomization using RECIST guidelines (version 1.1). Tumor assessments will be performed every 8 weeks, regardless of dose delays or dose interruptions, until investigator-assessed PD. Patients who come off study treatment prior to disease progression for reasons including patient or physician decision or unacceptable toxicity will continue to undergo tumor assessments every 8 weeks (<math>\pm 5</math> days) until investigator assessed PD. Patients will be treated according to local assessment of tumor scans.</p> <p>All patients will have a follow-up visit scheduled 30 days (<math>\pm 7</math> days) after the last dose of study treatment, regardless of reason for treatment termination. Patients will not be allowed to cross over from placebo to seribantumab. Survival follow up will be required for all patients every 2 months from the 30-day follow-up visit until death, loss to follow-up, withdrawal of consent, or study termination. After patients discontinue study treatment, subsequent</p>
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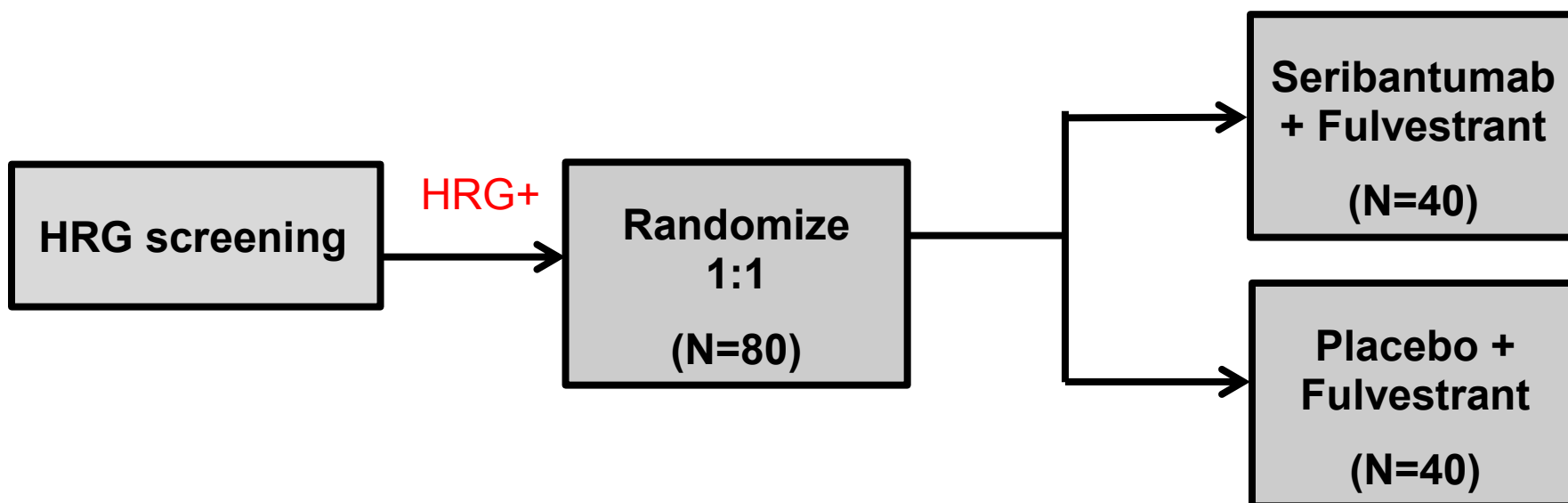
	<p>anti-cancer therapies will be collected according to the same schedule at the same time as survival follow-up.</p> <p>An independent Data Monitoring Committee (DMC) will be established to monitor emerging safety data and evaluate for trial efficacy. The DMC will regularly monitor safety data over the course of the study in accordance with the DMC Charter.</p>
<b>ESTIMATED # OF PATIENTS:</b>	Approximately 200 patients will be screened to enroll 80 HRG+ patients from an estimated 60-80 clinical trial sites from North America and Europe.
<b>STUDY POPULATION</b>	Women with metastatic ER/PR positive, HER2 negative, HRG positive breast cancer that has progressed following systemic therapy with a CDK inhibitor (e.g. palbociclib) in the locally advanced or metastatic disease setting. Patients cannot have received more than a total of two prior lines of therapy in the locally advanced or metastatic disease setting, and patients cannot have received chemotherapy in the locally advanced and metastatic disease setting. There is no restriction on chemotherapy use in the neoadjuvant or adjuvant setting.
<b>INCLUSION CRITERIA:</b>	<p>In order for inclusion, patients must have/be:</p> <ul style="list-style-type: none"> <li>• Histologically or cytologically confirmed ER+ and/or PR+ (with staining of <math>\geq 1\%</math> cells) breast cancer</li> <li>• Confirmed postmenopausal status due to either surgical/natural menopause or ovarian suppression (initiated at least 28 days prior to Day 1 of Cycle 1) with a gonadotropin-releasing hormone (GnRH) agonist, such as goserelin</li> <li>• HER2 negative per ASCO/CAP guidelines</li> <li>• A positive in-situ hybridization (ISH) test for heregulin with a score of <math>\geq 1+</math>, as determined by centralized testing of unstained tumor tissue</li> <li>• Must have at least one lesion amenable to either fresh tissue biopsy</li> <li>• Progressed following at least one but no more than two prior systemic therapies in the locally advanced or metastatic disease setting <ul style="list-style-type: none"> <li>○ Received prior CDK inhibitor based therapy for locally advanced or metastatic disease</li> </ul> </li> <li>• Documented progression of locally advanced or metastatic disease as defined by RECIST v1.1. <i>Exception:</i> patients with bone-only metastatic disease are eligible if they have at least 2 lytic lesions visible on a CT or MRI and have documented disease progression on prior therapy, based on RECIST v1.1 criteria. <ul style="list-style-type: none"> <li>○ Patients with bone-only lesions who have received radiation to those lesions must have documented progression following radiation therapy.</li> </ul> </li> <li>• Able to understand and sign an informed consent (or have a legal representative who is able to do so)</li> <li>• ECOG Performance Score (PS) of 0 or 1</li> <li>• Adequate bone marrow reserves as evidenced by: <ul style="list-style-type: none"> <li>○ ANC <math>&gt; 1500/\mu\text{l}</math></li> <li>○ Platelet count <math>&gt; 100,000/\mu\text{l}</math>; and</li> <li>○ Hemoglobin <math>&gt; 9 \text{ g/dL}</math></li> </ul> </li> <li>• Adequate hepatic function as evidenced by:</li> </ul>

	<ul style="list-style-type: none"> <li>○ Serum total bilirubin <math>\leq 1.5 \times \text{ULN}</math> except for patients with Morbus Gilbert</li> <li>○ Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and Alkaline Phosphatase <math>\leq 2.5 \times \text{ULN}</math> (<math>\leq 5 \times \text{ULN}</math> is acceptable if liver metastases are present, and <math>\leq 5 \times \text{ULN}</math> of Alkaline Phosphatase is acceptable if bone metastases are present)</li> <li>• Adequate renal function as evidenced by a serum creatinine <math>\leq 1.5 \times \text{ULN}</math></li> <li>• Recovered from clinically significant effects of any prior surgery, radiotherapy, or other antineoplastic therapy.</li> <li>• Patients may be treated with bone modifying agents such as bisphosphonates or receptor activator of nuclear factor kappa-B (RANK)-ligand agents (e.g. denosumab) per American Society of Clinical Oncology (ASCO) guidelines; whenever possible, patients requiring bone modifying agents should start treatment <math>\geq 7</math> days prior to study therapy and should continue the same agent throughout study unless clinically compelled to change</li> <li>• <math>\geq 18</math> years of age</li> <li>• Patients who have experienced a venous thromboembolic event within 60 days of signing the main consent form should have been treated with anti-coagulants for at least 7 days prior to beginning treatment and for the duration of treatment on this study.</li> </ul>
<b>EXCLUSION CRITERIA:</b>	<p>Patients must meet all the inclusion criteria listed above and none of the following exclusion criteria:</p> <ul style="list-style-type: none"> <li>• Prior treatment with an anti-ErbB3 antibody</li> <li>• Prior treatment with a chemotherapy in the locally advanced or metastatic disease setting</li> <li>• Patients cannot have received prior fulvestrant or other SERDs in the locally advanced or metastatic setting</li> <li>• Uncontrolled CNS disease or presence of leptomeningeal disease</li> <li>• Inflammatory breast cancer</li> <li>• History of another active malignancy that required systemic therapy in the last 2 years. Patients with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible.</li> <li>• Active infection, or an unexplained fever <math>&gt; 38.5^{\circ}\text{C}</math> during screening visits or on the first scheduled day of dosing, which in the investigator's opinion might compromise the patient's participation in the trial or affect the study outcome. At the discretion of the investigator, patients with tumor fever may be enrolled</li> <li>• Known hypersensitivity to any of the components of seribantumab, fulvestrant, or who have had hypersensitivity reactions to fully human monoclonal antibodies</li> <li>• Received other recent antitumor therapy including: <ul style="list-style-type: none"> <li>○ Investigational therapy administered within the 28 days or 5 half-lives, whichever is shorter, prior to the first scheduled day of dosing in this study</li> <li>○ Radiation or other standard systemic therapy within 14 days prior to the first scheduled dose in this study, including, in</li> </ul> </li> </ul>

	<p>addition (if necessary), the timeframe for resolution of any actual or anticipated toxicities from such radiation</p> <ul style="list-style-type: none"> <li>• NYHA Class III or IV congestive heart failure</li> <li>• Patients with a significant history of cardiac disease (i.e. uncontrolled blood pressure, unstable angina, myocardial infarction within 1 year or ventricular arrhythmias requiring medication) are also excluded</li> <li>• Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals; or active human immunodeficiency virus (HIV) infection, active hepatitis B infection or active hepatitis C infection</li> <li>• Any other medical condition deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, interfere with a patient's ability to cooperate and participate in the study, or interfere with the interpretation of the results</li> </ul>
<b>LENGTH OF STUDY:</b>	<p>A total study duration of approximately 20 months is expected. The primary analysis will be initiated when 58 PFS events have occurred.</p>
<b>STUDY TREATMENT(S):</b>	<p>Seribantumab/fulvestrant or placebo/fulvestrant (1:1)</p>
<b>INVESTIGATIONAL PRODUCT(S) FORMULATION:</b>	<p>Seribantumab is a clear liquid, supplied in sterile, single-use vials at a concentration of 25 mg/mL in 20 mM histidine, 150 mM sodium chloride, and pH 6.5. Seribantumab should be stored at 2-8°C.</p>
<b>ROUTE(S) OF ADMINISTRATION:</b>	<p>Seribantumab for intravenous (IV) infusion over 1 hour</p>
<b>NON INVESTIGATIONAL PRODUCT FORMULATION:</b>	<p>Fulvestrant solution for intramuscular injection (50 mg/mL) is commercially available. Fulvestrant is stored refrigerated at 2°-8°C (36°-46°F).</p> <p>Placebo: A clear liquid, supplied in sterile, single-use vials at a containing 20 mM histidine, 150 mM sodium chloride, at a pH of 6.5. Placebo should be stored at 2-8°C.</p>
<b>ROUTE(S) OF ADMINISTRATION:</b>	<p>Seribantumab and placebo: intravenous (IV) infusion over one hour Fulvestrant: intramuscular (IM) injection</p>
<b>DOSE REGIMEN:</b>	<p>Seribantumab 3 gm or matched placebo (120 mL) will be administered by intravenous infusion over 60 minutes on Days 1 and 15 of a 28 day cycle. Fulvestrant 500 mg will be administered intramuscularly on Days 1 and 15, and then Day 1 of each subsequent 28 day cycle.</p>
<b>SAMPLE SIZE/STATISTICAL CONSIDERATIONS:</b>	<p>The median PFS for the control arm (fulvestrant + placebo) is assumed to be 4.0 months in this patient population. A total of 58 PFS events will be required across two treatment arms randomized in a 1:1 ratio, giving approximately 80% power to detect a true hazard ratio of <math>HR \leq 0.57</math> (mPFS: 4 v 7), assuming a 1-sided significance level of 0.10. Approximately 200 patients will need to be screened in order to accrue 80 randomized in approximately 16 months with a total duration of 20 months.</p> <p><b>Primary Efficacy and Key Secondary Analysis:</b> The primary efficacy analysis will be performed using the Per Protocol (PP) population. PFS is defined as the number of months from the date of randomization to the date of the first documented objective disease progression (PD) using RECIST v1.1 or death due to any cause, whichever occurs first. If neither death nor progression is observed, data will be censored on the date of the last observed tumor assessment date. Patients without a valid tumor response evaluation at randomization will be censored</p>

	<p>on the date of randomization. Patients starting a new anti-cancer treatment prior to documented PD will be censored at the date of the last observed tumor assessment prior to start of the new treatment. Patients with documented PD or death after an unacceptable long interval (i.e., 2 or more missed or indeterminate scheduled assessments) will be censored at the time of the last observed tumor assessment date. PFS will be calculated as the date of the event/censor minus date of randomization plus one.</p> <p>The primary analysis will be performed using a stratified log-rank test comparing the PFS difference between two treatment arms. The final PFS analysis will preserve the 1-sided alpha at 0.10. Stratification factors will include bone-only disease (yes, no) and geographic status (US, and non-US). Kaplan-Meier estimates will be used to display PFS time graphically. Cox proportional hazards model will be used to estimate hazard ratio and the corresponding 80% confidence interval. Median PFS event times and 80% confidence interval will be computed as well.</p>
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## Study Schema



## 1. Introduction

### 1.1. Breast Cancer

Breast cancer remains one of the most common and deadly cancers in the United States, with an expected 231,840 newly diagnosed cases and 40,290 related deaths in 2015 alone ([American Cancer Society, 2015](#)). Among these, the largest molecular diagnostic subgroup (~70%) comprises of patients with hormone receptor positive (ER+/PR+; ER+/PR-; ER-/PR+) and HER2 negative (IHC <3+ and/or FISH negative) disease ([Onitilo, Engel, Greenlee, & Mukesh, 2009](#)). For patients with metastatic disease the reported median survival ranges from 18-36 months ([Eniu, Palmieri, & Perez, 2005](#)). Although metastatic breast cancer is not curable, meaningful improvements in survival have been seen, coincident with the introduction of newer systemic therapies ([Gennari, Conte, Rosso, Orlandini, & Bruzzi, 2005](#)).

### 1.2. Treatment for ER/PR positive HER2 Negative Advanced Breast Cancer

The general therapeutic principle for all patients with ER/PR positive metastatic breast cancer is aimed at prolonging survival and improving quality of life. This includes surgical intervention and the use of endocrine therapies for as long as possible to avoid the inherent toxicities of chemotherapy-based regimens. This is reflected in the current NCCN treatment guidelines that state: “systemic treatment of breast cancer recurrence or stage IV disease prolongs survival and enhances quality of life but is not curative. Therefore, treatments associated with minimal toxicity are preferred”.

Patients with metastatic disease have several first-line options where aromatase inhibitors (AIs) or fulvestrant are generally the preferred agents for first-line therapies as single agents. For postmenopausal patients with metastatic breast cancer who are endocrine therapy-naïve, progressing >12 months from the end of adjuvant therapy, or who present with *de novo* metastatic breast cancer, the options include an AI plus palbociclib or single-agent therapy using fulvestrant or an AI. Fulvestrant is a selective estrogen receptor down-regulator (SERD) and is indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal patients with disease progression following anti-estrogen therapy.

Palbociclib (formerly PD 0332991) is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK 4/6). Palbociclib plus letrozole received US Food and Drug Administration (FDA) accelerated approval as first-line therapy for metastatic ER-positive human epidermal growth factor receptor 2(HER2)-negative breast cancer in 2015 ([Finn et al., 2015](#)). Treatment with letrozole plus palbociclib resulted in a statistically significant increase in progression free survival (PFS) in the combination arm. Overall survival appeared favorable of the combination arm as well, but did not reach statistical significance. We would expect the majority of patients to receive this combination as their first line therapy where available before enrolling onto this study. Another combination option is available with the mechanistic target of rapamycin (mTOR) inhibitor everolimus for postmenopausal patients for the treatment of AI-resistant advanced ER+ breast cancer. In combination with exemestane, the benefit of everolimus was shown in the Breast Cancer Trials of Oral Everolimus (BOLERO-2) trial, which enrolled 724 patients who had progressed on anastrozole ([Baselga et al., 2012](#))([Piccart et al., 2014](#)). An improvement in PFS along with a higher ORR was observed for this combination but no statistically significant OS benefit was



observed at the time of the study publication or more recently in a follow up study on more mature OS data. The use of everolimus in an early line setting for advanced disease must be tempered by the significant adverse event profile observed in comparison to an AI alone. Patients are allowed to receive this combination prior to enrollment onto this study as well. There remains limited second-line and beyond endocrine therapy options in the metastatic setting with the AI, exemestane, being one of the more commonly used agents, and fulvestrant being another established option.

Innate and acquired resistance to endocrine therapy are significant therapeutic challenges in this context, as only those patients who have continuous sensitivity to endocrine therapy experience long-term survival with a reasonably good quality of life. Unfortunately, many patients develop resistance to endocrine therapy, resulting in very short treatment durations and the earlier need to move to cytotoxic chemotherapy, *especially in the second-line setting and beyond*. For patients who progress after two lines of endocrine therapy, treatment must be individualized based on their prior treatment response, tumor burden, and preferences for treatment. Finally, due to the obvious clinical benefits and positive tolerability profile of endocrine therapies in comparison to both, mTOR inhibitors and chemotherapies, identification and targeting of pathways which are mediating resistance to endocrine therapies is a thus far unmet clinical need.

### 1.3. Predictive Biomarkers for Response to Treatment

Endocrine therapies directed against the pro-proliferative effects of hormones in breast cancer are frontline treatments offering substantial survival benefits to breast cancer patients. Unfortunately, evolution of drug resistance in many patients lessens the clinical utility of this class of drugs (Harb, 2015). As discussed above, the identification of factors that can predict resistance or treatment failure is essential to guide patients to the correct drug treatments and courses of treatments. Personalized medicine aims to improve response rates and reduce mortality by getting the right patients the correct drug.

Endocrine therapy resistance can be classed as broad endocrine resistance or agent specific, where a tumor does not entirely rely on hormonal signaling or in the latter case changing to alternative anti-hormonals can still elicit significant responses (Dalmau, Armengol-Alonso, Muñoz, & Seguí-Palmer, 2014). Multiple molecular mechanisms of resistance have been described and investigated in the preclinical setting and followed up by analysis of archived tissues (Simon, Paik, & Hayes, 2009). Such mechanisms include ER $\alpha$  protein levels, phosphorylation status, PR protein expression, cell cycle regulator expression changes and hormone level changes due to metabolism. In addition, activation of growth factor pathways has also been implicated in endocrine treatment resistance, where MAPK and PI3K activation leads ER $\alpha$  independent growth or can via cross-talk with ER $\alpha$  promote treatment resistance (Hayes & Lewis-Wambi, 2015). For example, examination of HER1, HER2 and HER3 levels in the tamoxifen and exemestane adjuvant multinational (TEAM) trial revealed that only patients with HER1-3 negative tumors had a decreased risk of relapse when receiving exemestane versus tamoxifen (Bartlett et al., 2013). However, the validation of a biomarker in a randomized clinical trial that faithfully predicts the activation of such pathways and thus the emergence of resistance is currently not available to fully guide the selection of endocrine therapy for real time benefits to patients (Beelen, Zwart, & Linn, 2012). Neither the BOLERO-2 study nor the PALOMA trials have identified a mechanistic

biomarker able to predict which patients will respond to the respective combinations, and which are at risk of early disease progression and therapeutic failure.

Identification and implementation of clinically relevant biomarkers that help physicians guide patients treatment programs in ER/PR positive advanced breast cancer are urgently needed and represent a highly relevant unmet need in this indication.

Available pre-clinical and clinical data suggests that the ErbB3-AKT signaling pathway may be a key player in mediating such resistance to endocrine therapies. In addition, Merrimack has demonstrated that the addition of seribantumab, an ErbB3 directed monoclonal antibody, to endocrine based therapies could potentially bring an improved endocrine based treatment option to patients who have been selected based on the presence of heregulin (HRG) in their tumors.

#### 1.4. ErbB3

ErbB3 was first isolated and characterized in 1989 ([Kraus et al., 1989](#)). The ErbB3 receptor is a 148 kilodalton (kDa) transmembrane receptor tyrosine kinase belonging to the ErbB/EGFR family and was shown to be kinase dead ([Citri et al., 2003](#)). The ErbB family of transmembrane receptor tyrosine kinases impacts the physiology of cells and organs by eliciting ligand-dependent activation of multiple signal transduction pathways. Upon binding of HRG, the physiological ligand for the ErbB3 receptor, ErbB3 dimerizes with other ErbB family members, preferentially ErbB2.

Heregulin, the cognate ligand to ErbB3, has been shown to be involved in several different types of cancer: breast, ovarian, endometrial, colon, gastric, lung, thyroid, glioma, medulloblastoma, melanoma, as well as squamous cell carcinomas of the head and neck ([Breuleux, 2007](#); [Stove & Bracke, 2005](#)). In most of these tumor types, HRG regulates growth, invasion, and angiogenesis through the presence of either autocrine or paracrine HRG signaling. It is thought that autocrine HRG may give rise to constitutively activated ErbB2 and ErbB3, protecting these tumors against apoptosis and generating growth factor independence ([Li et al., 2004](#); [Mills & Yarden, 2010](#); [Sheng et al., 2010](#)). Disruption of the heregulin autocrine loop by blocking HRG binding to ErbB3 or disruption of the ErbB2/ErbB3 dimer is considered to provide an important therapeutic measure to control cancer cell growth ([Yarden & Pines, 2012](#); [Yarden & Sliwkowski, 2001](#)).

An important defining feature of the ErbB network is that two members of the family, ErbB2 (also known as HER2/neu) and ErbB3, are non-autonomous. ErbB2 lacks the capacity to interact with the growth-factor ligand, whereas the kinase activity of ErbB3 is defective. Despite this lack of autonomy, both ErbB2 and ErbB3 form heterodimeric complexes with other ErbB receptors that are capable of generating potent cellular signals. Mechanistic details of this pathway are summarized below.

- HRG is a ligand for ErbB3, where ErbB2 is the main binding and activation partner upon ligand binding.
- The role of ErbB3 and HRG in the development and progression of multiple cancers is becoming better established in patients. Indeed, it has recently been shown that ErbB3 levels are associated with shorter disease-free survival in patients with invasive breast carcinoma. ErbB3 expression has also recently been shown to be predictive of poor prognosis in multiple cancers.
- Dimerization of ErbB3 with other ErbB family members results in transphosphorylation of ErbB3 on tyrosine residues, six consensus YXXM tyrosine phosphorylation motifs,

contained with the cytoplasmic tail of the protein. Such signaling activated downstream pathways including MAPK and PI3K/AKT that are known to play a role in cancer. (Dey, Williams, Leyland-Jones, & De, 2015)

- In addition to the effects of ErbB3 and its ligands on the pathophysiology of multiple malignancies, they are also believed to be integrally involved in the resistance of several tumor types to targeted therapies or chemotherapy. (Ma, Lyu, Huang, & Liu, 2014)
- Pioneering studies have demonstrated that high expression of ErbB3 can predict early escape from the anti-ErbB2 monoclonal antibody trastuzumab. Moreover, ErbB3 expression has also been associated with resistance to anti-estrogen therapy (Arteaga & Engelman, 2014)

Therefore, monoclonal antibodies like seribantumab that can target the ligand binding domain of ErbB3 may represent a novel anti-neoplastic strategy. Based on the data presented in this document, Merrimack believes that targeting the ligand binding domain of ErbB3 is a promising strategy in HR-positive, HER2-negative mBC.

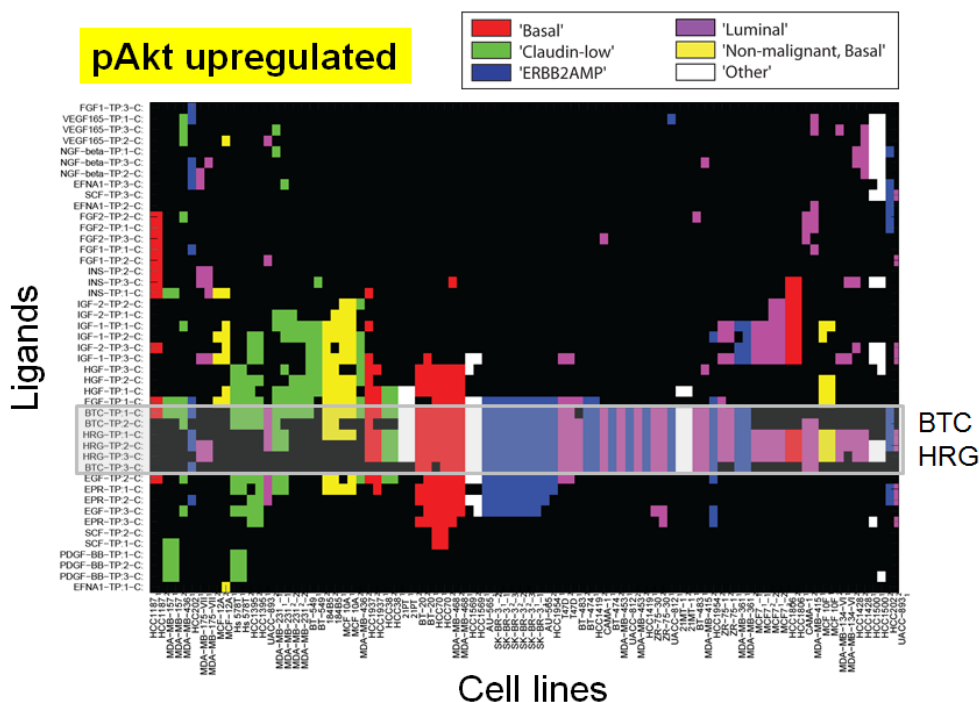
### 1.5. Seribantumab

Seribantumab is a fully human, monoclonal IgG2 antibody that binds to the HRG domain of the ErbB3 receptor with single digit nanomolar affinity and is being developed as an anti-cancer therapeutic. By preventing HRG from binding to the ErbB3 receptor, seribantumab effectively blocks heterodimer formation of the ErbB3 receptor with e.g. ErbB2 and EGFR and potentially blocks downstream signaling activation and cancer cell survival. Merrimack Pharmaceuticals originally identified the ErbB3 receptor as a novel therapeutic target using a systems biology approach which allows for a holistic understanding of the dynamics of a specific signaling pathway by applying mechanistic computational models and quantitative biology (Rajkumar, Stamp, Hughes, & Gullick, 1996; Schoeberl, Eichler-Jonsson, Gilles, & Müller, 2002; Sheng et al., 2010). In addition, the insights gained by computer simulations were also used to generate a preclinical biomarker hypothesis that was tested clinically in previous randomized Phase 2 studies and led to the identification of HRG as the principal biomarker for seribantumab efficacy.

#### 1.5.1. Pre-Clinical Experience of Seribantumab in Breast Cancer

In order to identify the most potent pathways that are critical for cancer progression, AKT phosphorylation was analyzed as a surrogate marker in the National Cancer Institute (NCI)-60 panel of 60 cell lines (59 presently available) derived from several different cancer types. These include leukemias, melanomas, ovarian, renal, prostate, colon, lung, and central nervous system (CNS) cancers. Each of the cell lines in the NCI-60 panel was stimulated with 60 different ligands (cytokines, chemokines, hormones, and growth factors), and AKT phosphorylation was assessed by enzyme-linked immunosorbent assay. The results showed that HRG1-β1 and the epidermal growth factor-like ligands are very potent activators of AKT signaling as compared to other growth factors or chemokines. This data indicates that the HRG family of ligands are some of the strongest inducers of AKT phosphorylation, which is a prosurvival signal. (Schoeberl et al., 2002)

**Figure 1: Pro-survival AKT Signaling is Activated by ERBB3 Ligands**

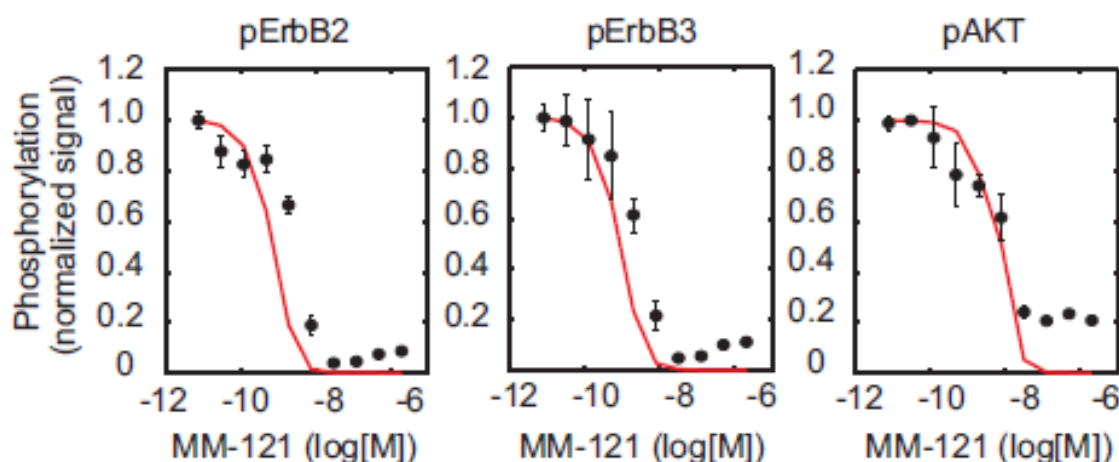


The NCI-60 cell panel was screened for AKT activation in response to stimulation with multiple growth factor ligands.

#### 1.5.1.1. Seribantumab is a Potent ErbB3 Antagonist

Based on the results from the sensitivity analysis, the ErbB3 inhibitor simulations, and experimental data, we identified ErbB3 as a potential therapeutic target and developed seribantumab, a fully human IgG2 mAb that binds specifically to ErbB3. The dissociation constant (K<sub>d</sub>) for seribantumab was determined to be 769 pM, with an association rate of  $1.43 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$  and a dissociation rate of  $1.10 \times 10^{-4} \text{ s}^{-1}$  measured by kinetic exclusion assay (KinExA). The signal inhibitory activity of seribantumab is shown in [Figure 2](#), where cells were stimulated with HRG in the presence of varying concentrations of seribantumab and phosphorylated ErbB2 and ErbB3 and the downstream effector AKT was measured. This data illustrates that seribantumab is an effective ErbB3 pathway agonist.

**Figure 2: Seribantumab Inhibits HRG-mediated Signaling Through the ErbB2-ErbB3-AKT Signaling Pathway**

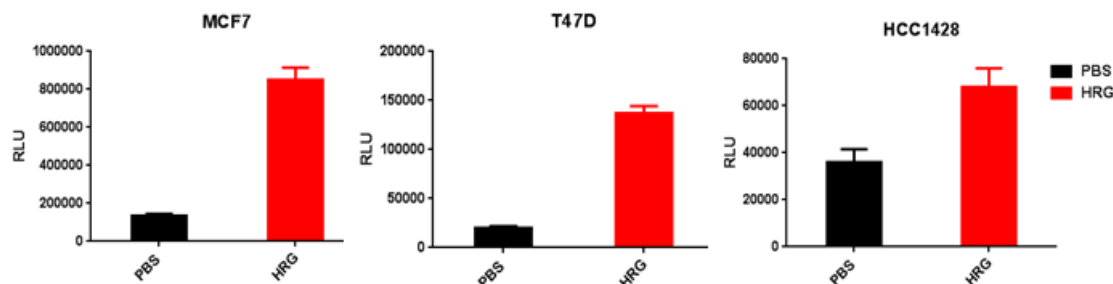


Cells were treated with seribantumab for 1.5 hours and then stimulated with HRG for 10 min after which tyrosine phosphorylated ErbB2 & ErbB3 and serine phosphorylated AKT was measured.

#### 1.5.1.2. Heregulin stimulation promotes Estrogen Receptor Positive Breast Cancer Cell Line Proliferation

To explore the effect of the ErbB3 ligand, HRG on proliferation, we tested the HR-positive, HER2-negative cells lines MCF7, T47D and HCC1428 using an established CTG assay that measures cellular ATP as an indicator of viability. We found that HRG stimulated proliferation of all of the HR-positive, HER2-negative cells lines *in vitro*, indicating that HRG may be a ligand promoting proliferation of this type of breast cancer. This finding is relevant to this particular indication as HRG mRNA has been found in approximately 40 to 50% of advanced breast cancer patients' tumor samples. In addition, other cancer indications such as HNSCC, HRG mRNA is found in more than 90% of patient tumor samples

**Figure 3: HRG Promotes Proliferation of HR-positive, Her2-negative Breast Cell Lines**



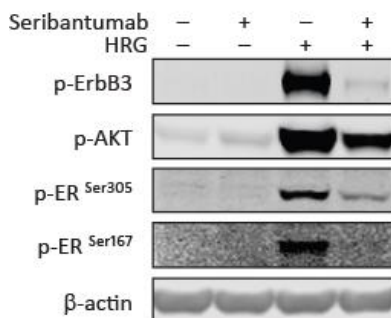
Cells were stimulated with HRG for 6 days and proliferation was measured by CTG assay.

#### 1.5.1.3. Heregulin stimulation of ErbB3 promotes Estrogen Receptor Phosphorylation

To explore the effect of inhibiting HRG-mediated ERBB3 signaling on ER phosphorylation, we stimulated MCF-7Ca cells, which exogenously express the CYP19 aromatase gene, in vitro with HRG, in the presence and absence of seribantumab, and measured phosphorylated protein levels

by immunoblotting. Treatment with HRG potently stimulated ERBB3 and AKT phosphorylation, as well as ER phosphorylation at serine 167 and serine 305 (Figure 4), indicating direct cross-talk between the ErbB3 and ER signaling pathways in this cell line. Treatment with seribantumab reduced HRG-stimulated phosphorylation of ErbB3, AKT and ER in MCF-7Ca cells.

**Figure 4: Heregulin Activates ER Phosphorylation in MCF-7Ca Cells**

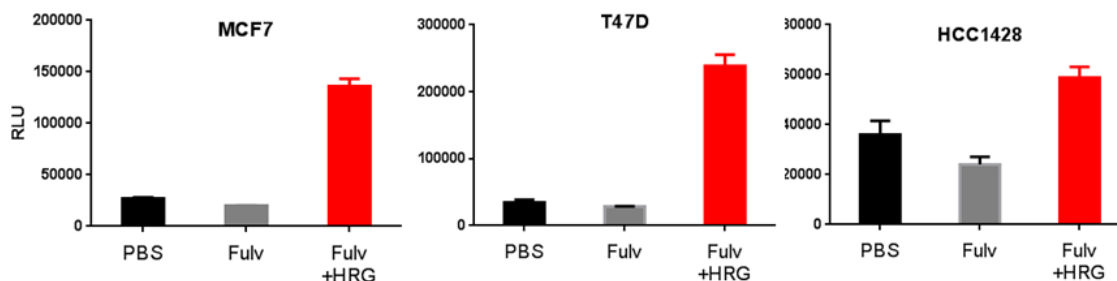


Serum-starved MCF-7Ca cells were pre-treated with seribantumab (Seri; 1  $\mu$ M) for 1 h, followed by treatment with 10 nM HRG for 10 min

#### 1.5.1.4. Heregulin Blocks the Anti-hormonal Activity of Fulvestrant

Based on our findings that HRG stimulates the proliferation of HR-positive cell lines and that HRG-ErbB3 signaling promotes phosphorylation and activation of the estrogen receptor, we next wanted to evaluate the effect such activation had on the activity of anti-hormonal drugs. We chose the clinically relevant anti-hormonal, fulvestrant as it has a dual mechanism of action, whereby it blocks binding of estrogen to the estrogen receptor and also promotes its degradation and is approved for the treatment of HR-positive, HER2-negative advanced breast cancers.

**Figure 5: HRG Blocks the Activity of Fulvestrant in HR-positive, HER2-negative Cell Lines**



Cells were stimulated with HRG for 6 days and proliferation was measured by CTG assay

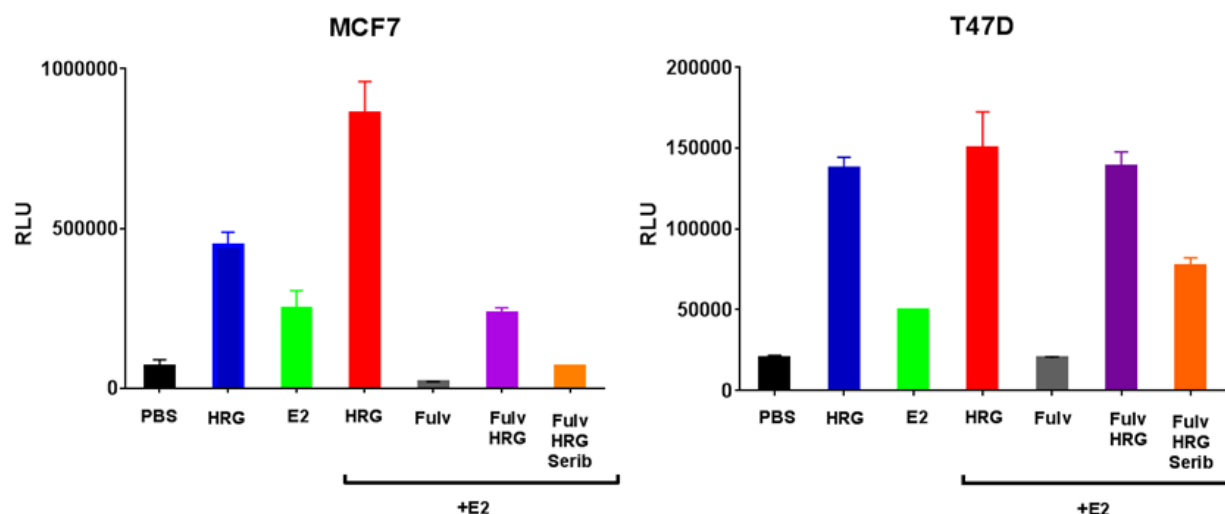
As shown in Figure 5, we found that HRG could block the anti-proliferative effects of the anti-hormonal, fulvestrant in MCF7, T47D and HCC1428 cell lines when proliferation was measured *in vitro*. These findings suggested that HRG-ErbB3 signaling may be an anti-hormonal resistance mechanism in cancer cells that show activation of this pathway and prompted us to evaluate inhibition of this signaling axis with seribantumab.



### 1.5.1.5. Heregulin Blocks the Anti-hormonal Activity of Fulvestrant and Blocking ErbB3 with Seribantumab Restores Sensitivity

Based on our previous findings that HRG could block the anti-hormonal activity of fulvestrant, even in the absence of exogenously added estrogen, we next examined the effect of blocking HRG binding to ERBB3 with seribantumab. In this experiment, we added to both HRG and estrogen to challenge the system fully. [Figure 6](#) shows that the addition of estrogen to cells increases the proliferation rate considerably in both of the cellular models. As would be expected, fulvestrant significantly inhibits the estrogen induced increase in proliferation. However, the addition of HRG to cells treated with both estrogen and fulvestrant, shows considerable inhibition of fulvestrant activity, which is in agreement with our previous data demonstrating that HRG mediates insensitivity to fulvestrant in these cellular models ([Figure 5](#)). Finally, when we treated cells with seribantumab in the presence of estrogen and HRG we found that fulvestrant activity was almost restored completely. Taken as a whole, this data set indicates that the HRG-ErbB3 signaling axis may be promoting insensitivity to anti-hormonal agents such as fulvestrant and these findings are in agreement with data published from other groups that suggest that inhibiting this signaling pathway may offer benefit to patients who have HRG present in their tumors ([Morrison et al., 2013](#))([Hutcheson et al., 2011](#)).

**Figure 6: HRG Blocks the Activity of Fulvestrant in HR-positive, Her2-negative Cell Lines and Seribantumab Restores Fulvestrant Sensitivity**



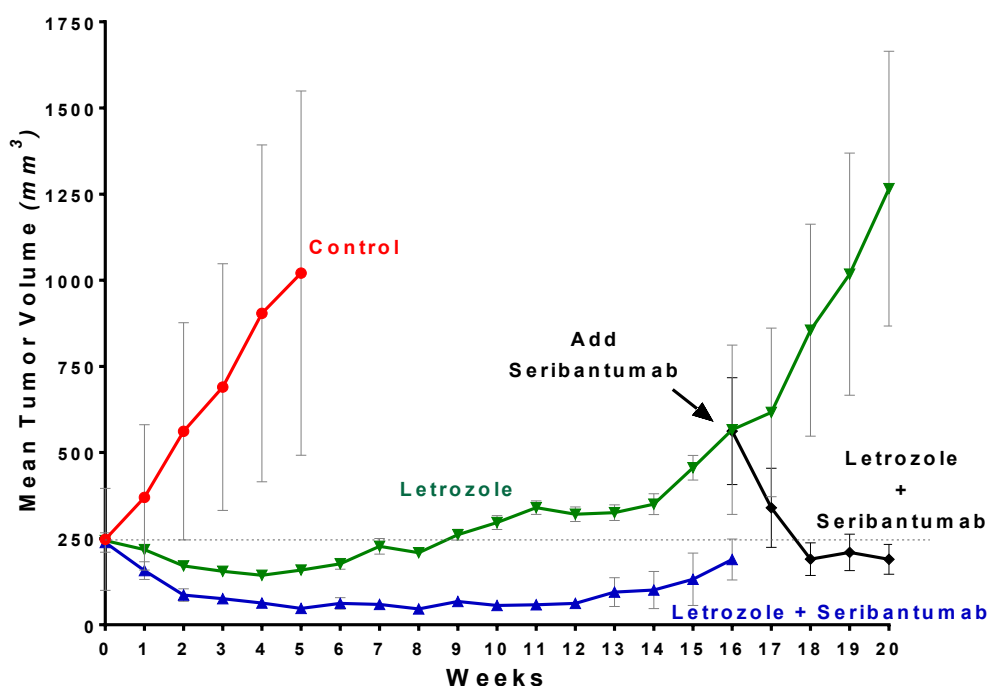
Cells were stimulated with HRG for 6 days and proliferation was measured by CTG assay

### 1.5.1.6. Combination of Aromatase Inhibitor and Seribantumab in a HR+ Breast Cancer Xenograft Model

HER2 and HER3 signaling have previously been implicated in the development of resistance to anti-estrogens such as tamoxifen, and inhibition of ErbB3 signaling was shown to overcome HER2-mediated tamoxifen resistance in ER+ breast cancer cells. More recently, studies using an *in vivo* model of post-menopausal ER+ breast cancer indicated that the development of resistance to the non-steroidal AI letrozole was associated with up-regulation of HER2 expression in xenografts([Curley et al., 2015](#)).

In this study, we used this same model of post-menopausal ER+ breast cancer to determine the effect of blocking HRG-mediated ERB3 signaling and /or estrogen-mediated ER activation on tumor growth (Figure 7). MCF-7Ca xenograft tumors were generated in female, ovariectomized nude mice, which were randomized to receive vehicle (“Control”; 0.3% hydroxypropylcellulose (HPC) in 0.9% NaCl, twice weekly (Q2W), intraperitoneal injection (IP); 15 mice/group), seribantumab (750 µg/mouse, Q2W, IP; 15 mice/group), letrozole (10 µg/mouse/day x 5 days/week (QD x 5), subcutaneous injection (SQ); 60 mice/group), or letrozole in combination with seribantumab, dosed as indicated for the monotherapies (15 mice/group). Changes in mean tumor volume ( $\pm$  SEM) were determined weekly by caliper measurement. Following the development of resistance to letrozole (week 14), mice in the letrozole-only group were re-randomized into 15 mice/group to receive: letrozole alone; seribantumab alone; or a combination of letrozole and seribantumab.

**Figure 7: Seribantumab and Letrozole Co-treatment Delays the Onset of Resistance and Restores Sensitivity to Letrozole in MCF-7Ca Xenografts**



The MCF-7Ca–derived xenograft tumors initially responded to letrozole, but started to develop resistance after approximately 7-8 weeks of treatment (Figure 7). When mice were co-treated with letrozole and seribantumab, however, tumor growth was inhibited and resistance to letrozole substantially delayed (Figure 7). This suggests that HRG/ERBB3 signaling was either active at the outset of the study or developed relatively quickly in response to letrozole treatment. Once resistance to letrozole was clearly established (week 14), mice in the letrozole-treated group were re-randomized to one of two cohorts: (i) continued letrozole monotherapy or (ii) seribantumab in combination with letrozole (Figure 3). Notably, the letrozole-resistant tumors displayed significantly decreased tumor growth when co-treated with letrozole and seribantumab compared to treatment with letrozole alone (Figure 3). This is consistent with the hypothesis that



blocking both estrogen/ER- and HRG/ErbB3-driven signaling provides greater antitumor activity than blocking either pathway alone

The implications of combining seribantumab and letrozole are that targeting ErbB3 signaling in ER+ breast cancer tumors that express HRG may extend the activity of AIs in post-menopausal ER+ breast cancer patients after they have progressed on monotherapy AI. Furthermore, it is also tempting to speculate that the addition of seribantumab immediately upfront with an AI may delay the onset of resistance in these patients, a hypothesis that requires testing in a clinical trial setting.

### **1.5.2. Clinical Experience of Seribantumab in Humans**

Seribantumab has been studied in eight previous clinical trials under IND #100605 with a total of 700 patients being exposed to seribantumab alone or in combination with other anti-cancer therapies. The first trial was a phase 1 open label, dose escalation study using a modified “3 + 3” design. Six cohorts of patients were enrolled (n=25), at doses of 3.2, 6, 10, 15 and 20 mg/kg and a 40 mg/kg loading dose followed by 20 mg/kg weekly maintenance dosing, and an expansion cohort of patients was enrolled at 20 mg/kg with a 40 mg/kg loading dose. At the close of the study, 43 patients were exposed to seribantumab. A Maximum Tolerated Dose (MTD) was not identified, and the highest dose tested was 40 mg/kg loading dose followed by 20 mg/kg on a weekly dosing schedule.

Several other seribantumab trials were initiated in varying indications and chemotherapy combinations. Investigators should refer to the seribantumab Investigator’s Brochure for more information regarding ongoing and previous trials of seribantumab. Previous experiences in breast cancer and safety of seribantumab in combination with endocrine therapies are described in more detail below.

#### **1.5.2.1. Previous Experience of Seribantumab in Metastatic Breast Cancer**

Seribantumab was tested in combination with exemestane in a previous placebo-controlled Phase 2 study in post-menopausal patients with ER/PR+, Her2 negative breast cancer. Using a dose of seribantumab as determined from a Phase 1 dose escalation study, patients were randomized to receive 25 mg exemestane daily in combination with either 20 mg/kg weekly seribantumab (with a 40 mg/kg loading dose) (N=59) or placebo (N=59) as presented at the American Society of Clinical Oncology (ASCO) ([Higgins et al., 2014](#)). The primary efficacy objective of achieving a 50% reduction in hazard ratio in the Seribantumab group vs. the placebo group was not reached. The estimated median PFS was 15.9 weeks for the seribantumab group vs. 10.7 weeks in the placebo group, resulting in a hazard ratio of 0.772 (p=0.2486).

A pre-planned biomarker analysis using archived tissue samples obtained from patients enrolled in the study showed that patients who had HRG positive tumors (as determined by RT-PCR testing) had an increased risk of progression when receiving exemestane alone in comparison to those patients who had HRG negative tumors. Patients with HRG positive tumors seemed to benefit from the addition of seribantumab to exemestane. These data are described in detail in Section 1.4.

Additionally, seribantumab was tested in combination with paclitaxel in a previous Phase 2 study in patients with either locally advanced, pre-operative hormone receptor positive and Her2 negative breast cancer (N=101). Patients were randomized to receive either a 2- week run-in of

seribantumab followed by 4 weeks of weekly seribantumab in combination with paclitaxel or 4 weeks of weekly paclitaxel alone. Both groups of patients were then treated biweekly with 4 cycles (8 weeks) of doxorubicin in combination with cyclophosphamide and subsequently underwent surgery. The primary efficacy readout was pathologic complete response rate (pCR). Patients on the Seribantumab arm had a pCR rate of 10.1% (7/66) and patients on the control arm had a pCR rate of 3.3% (1/33). No formal hypothesis testing was done in this study.

### **1.5.3. Potential Toxicities with Seribantumab**

The safety profile of Seribantumab has been robustly studied across nine previously conducted clinical trials, conducted as a monotherapy and in combination with various targeted and cytotoxic therapies.

Findings from trials of seribantumab in human subjects are comprised of safety data from 962 patients that have been enrolled into seribantumab studies under the IND #100605, including 700 patients that have been exposed to seribantumab alone (n=43) or in combination with other anti-cancer therapies (n=657). Treatment-emergent adverse events (TEAEs) were reported in 98.9% of patients, regardless of relationship to study treatment. More than half the patient population reported TEAEs in the following systems organ class: gastrointestinal disorders (88.9% treatment, 74.8% control), general disorders and administration site conditions (78.7% treatment, 72.1% control), skin and subcutaneous tissue disorders (75.9% treatment, 64.1% control), metabolism and nutrition disorders (59.3% treatment, 45.0% control), respiratory, thoracic and mediastinal disorders (57.4% treatment, 45.4% control), nervous system disorders (57.1% treatment, 54.2% control), and infections and infestations (53.4% treatment, 46.9% control).

As of July 2014, the most frequently occurring (>20% of patients) treatment emergent adverse events across all patients exposed to seribantumab as single agent or in combination therapies included: diarrhea (70.3%), fatigue (51.9%), nausea (45.4%), rash (32.9%), decreased appetite (29.7%), alopecia (26.4%), anemia (24.9%), vomiting (24.9%), hypokalemia (22.6%), stomatitis (22.3%), and peripheral neuropathy (20.1%).

A breakdown of safety data by study is presented in the Investigator Brochure, including a separate study of 27 patients of seribantumab in combination with a PI3K-inhibitor, XL147, which was conducted by a different Sponsor. Toxicities observed with combinations relevant to this study are further summarized below.

#### **1.5.3.1. Previous Safety Experience of Seribantumab in Combination with Endocrine Therapies**

Seribantumab has been combined with exemestane in one previous placebo-controlled study, and 56 patients were dosed with the combination. In this study, the most frequently reported adverse events (reported in  $\geq 15\%$  of patients) regardless of relationship included (treatment arm % vs. control arm %): diarrhea (50.0% vs 23.7%), nausea (28.6% vs 23.7%), fatigue (25.0% vs 23.7%), arthralgia (21.4% vs 20.3%), cough (16.1% vs 16.9%), and decreased appetite (16.1% vs 10.2%). The most frequently reported adverse events (reported in  $\geq 15\%$  of patients) that were assessed by the Investigator to be related to seribantumab include: diarrhea (37.5% vs 11.9%), fatigue (19.6% vs 13.6%), and nausea (16.1% vs 18.6%).

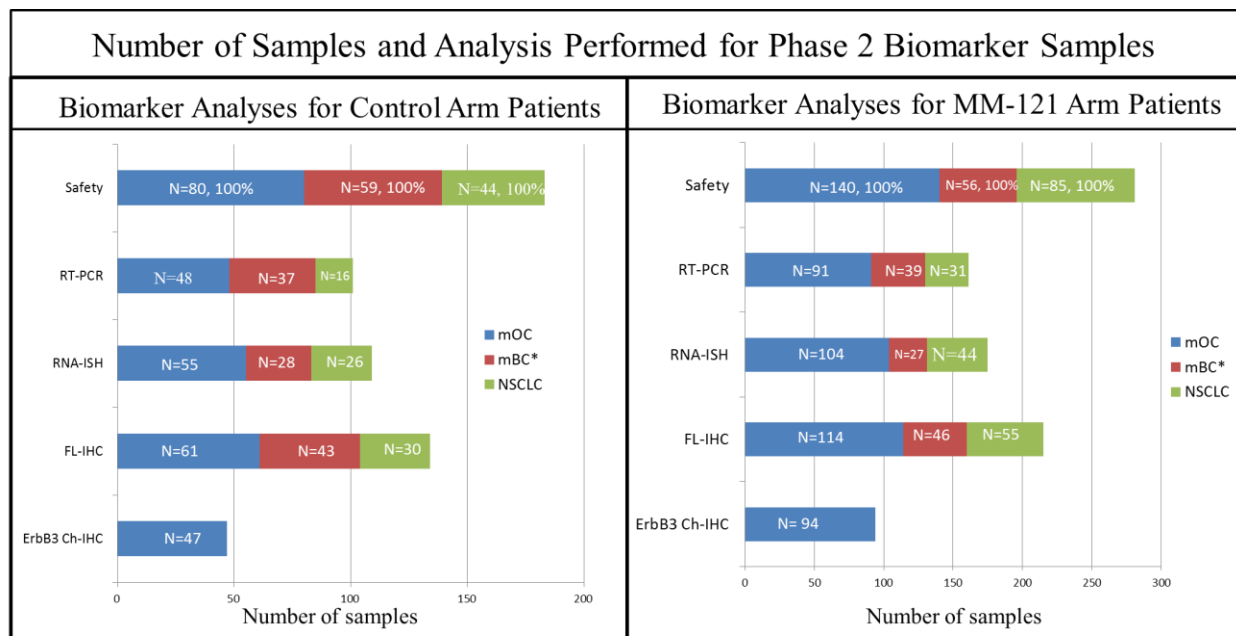
Serious adverse events were reported in 7 patients (12.5%) on the seribantumab plus exemestane arm compared to 11 patients (18.6%) on the control arm. The most frequently reported serious event on the seribantumab containing arm was nausea, occurring in 2 patients (3.6%).

Seribantumab has not been combined with fulvestrant in other clinical studies. It is expected that seribantumab will continue to combine well with endocrine agents and with no expected increases in frequencies of severe or serious adverse events. Increased reports of mild to moderate AEs may be observed for diarrhea, nausea, vomiting, and fatigue.

## 1.6. Study Rationale

Across the three randomized studies conducted with seribantumab in metastatic hormone receptor positive, HER2 negative breast cancer (mBC), platinum resistant ovarian cancer (mOC) and EGFR wild-type NSCLC that has progressed following a platinum based front-line therapy for metastatic or locally advanced disease, a consistent finding emerged: high mRNA levels of HRG appeared to be predictive of poor outcome when patients received only the standard of care treatment (exemestane (mBC), paclitaxel (mOC) or erlotinib (NSCLC)) (Figure 8). However, the data also suggested that the addition of seribantumab to exemestane, paclitaxel and erlotinib significantly improved progression free survival in patients who had HRG positive tumors (Figure 8). These data have been presented at ASCO and ESMO (Higgins et al., 2014; Liu et al., 2014; Sequist et al., 2014), and Table 1 provides a summary for the findings in the overall study population and the HRG positive subgroups. A summary of the number of the samples and the types of assays performed on the biomarker samples received are presented in Figure 8.

**Figure 8: Number of Biomarker Samples Collected and the Analysis Performed for the Three Randomized**



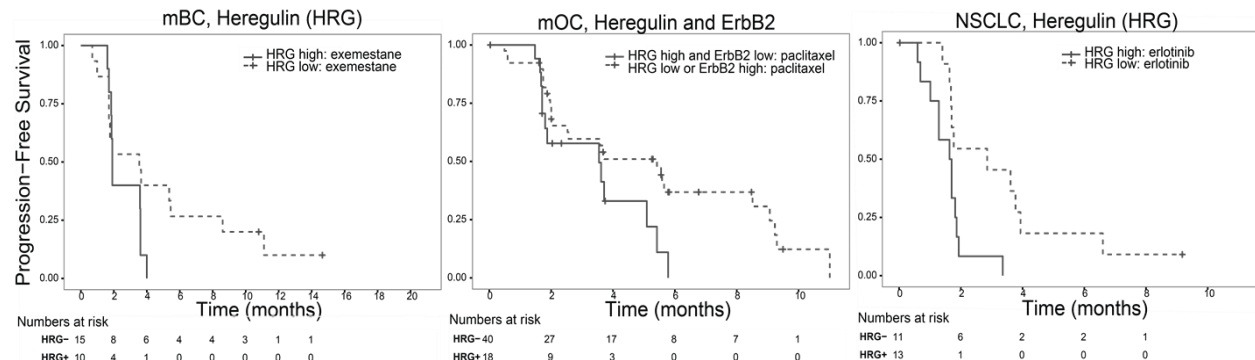
\* Biomarker data for the mBC population are derived from archived tissue vs. fresh tissue obtained from the mOC and NSCLC patients

## Phase 2 Studies of Seribantumab

The results from these pre-planned retrospective analyses were consistent with the hypothesis that blockade of HRG-induced ErbB3 signaling by seribantumab can restore sensitivity to

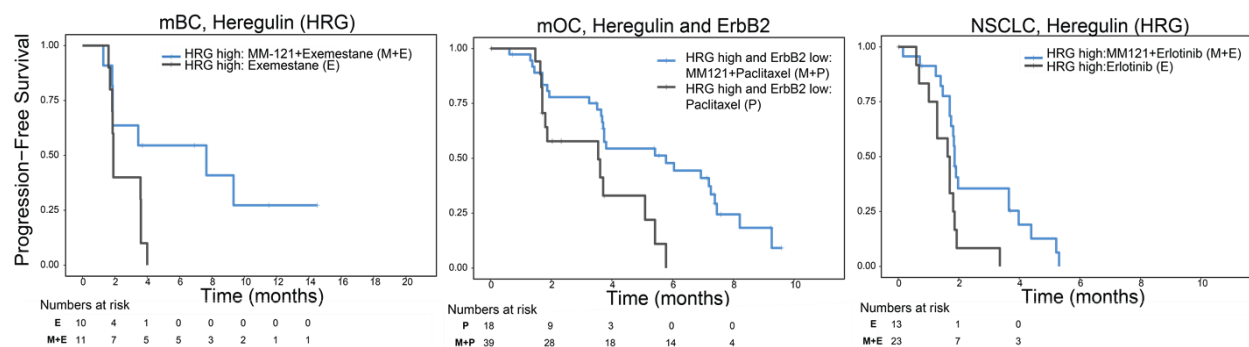
standard of care agents impacted by HRG. However, prospective selection of the relevant patient population is needed to validate these findings. A comprehensive review of the results from the completed seribantumab Phase 2 studies further suggested that the effect of the seribantumab-mediated blockade of HRG signaling is particularly effective in the context of endocrine therapies, as these therapeutic backbones have the potential for substantial baseline efficacy in patients with endocrine sensitive disease.

**Figure 9: Positive HRG mRNA Levels Identify a Subgroup of Patients with an Increased Risk of Progression on Standard-of-care Therapies**



HRG mRNA was measured from fresh tumor biopsies using RNA in-situ hybridization (ISH) in the mOC and NSCLC studies and HRG positive was defined as staining positive (noted as “high” in the figure) and HRG negative (noted as “low” in the figure) as staining negative. In the mBC study HRG was measured using quantitative RT-PCR from archived tissue and HRG positive was defined as negative delta CT > -5. HER2 expression was measured using quantitative immunohistochemistry in mOC and HER2 low was defined as < 125892 receptors per cell which corresponds to an estimate of HER2 2+ using conventional HercepTest™. The three Kaplan-Maier plots show Risk of Progression estimates for patients with either high or low HRG mRNA levels in NSCLC (erlotinib), mOC (paclitaxel), and mBC (exemestane).

**Figure 10: Treatment Effect of Seribantumab in Patients with HRG Positive Tumors**



The addition of seribantumab consistently extended progression-free survival in patients with positive HRG mRNA levels (solid lines all graphs). Patients with mOC were also selected for low HER2 expression. Patients in the mBC and NSCLC study were HER2 low in accordance with inclusion criteria (mBC) or disease biology (NSCLC).

**Table 1: Summary Statistics for Experimental Treatment vs. Control PFS in HRG Positive Subgroup**

Study group	N	Prev <sup>a</sup>	Seribantumab treatment arm vs. control arm in HRG positive subgroup			Seribantumab Arm		Comparator Arm	
			HR	95%CI	P	Events n (%)	PFS time (months) Median	Events n (%)	PFS time (months) Median
<i>mBC (exemestane +/- Seribantumab)</i>	21	37%	<b>0.32</b>	0.11-0.97	<b>0.044</b>	7 (63.6)	7.7	10 (100)	1.9
mOC (paclitaxel +/- Seribantumab) <sup>b</sup>	57	38%	<b>0.37</b>	0.18-0.79	<b>0.009</b>	26 (66.7)	5.8	13 (72.2)	3.5
NSCLC (erlotinib +/- Seribantumab)	36	54%	<b>0.37</b>	0.17-0.82	<b>0.014</b>	20 (87.0)	1.9	12 (92.3)	1.7

<sup>a</sup> Prev = Prevalence of HRG positive subpopulation calculated from overall study population

<sup>b</sup> In mOC the biomarker predicting benefit was a combination of HER2<sup>low</sup> and HRG positive

### 1.6.1. Previous Experience in Heregulin Negative Patients

In contrast to the data from the previous three randomized Phase 2 studies indicating that heregulin positive patients perform poorly on control treatments, patients whose tumors are negative for heregulin were consistently shown across the three trials to perform relatively well on control treatments. The data further suggested that, in mOC and NSCLC, patients with HRG negative tumors performed better on control than on the experimental arm. The statistics of the three Phase 2 studies summarized in Table 2 suggest that further development of seribantumab should focus on patients with HRG positive tumors.

**Table 2: Summary Statistics for Experimental Treatment vs. Control PFS in HRG Negative Subgroup**

Study Group	Seribantumab treatment arm vs. control arm in HRG <sup>low</sup>			HRG <sup>low</sup> Seribantumab arm		HRG <sup>low</sup> control arm	
	HR	95%CI	P	Events n (%)	PFS time (months) median	Events n (%)	PFS time (months) median
<i>mBC (exemestane +/- Seribantumab)</i>	<b>1.06</b>	0.51-2.19	<b>0.87</b>	17 (81.0)	2.4	13 (86.7)	3.5
mOC (paclitaxel +/- Seribantumab) <sup>a</sup>	<b>1.54</b>	0.98-2.44	<b>0.062</b>	65 (90.3)	3.5	27 (67.5)	5.4
NSCLC (erlotinib +/- Seribantumab)	<b>2.43</b>	1.07-5.55	<b>0.034</b>	19 (95.0)	1.6	10 (90.0)	2.9

<sup>a</sup> In mOC the biomarker predicting benefit was a combination of HER2<sup>low</sup> and HRG<sup>high</sup>

### 1.6.2. Summary of Study Rationale

Identification and treatment of resistance to endocrine therapies remains an unmet therapeutic need for patients with ER/PR positive, HER2 negative breast cancer in the advanced/ metastatic setting. This resistance to endocrine therapies often conflicts with the current treatment paradigm that is reflected in the NCCN treatment guidelines which asks for the use of well tolerated endocrine therapies as long as possible in the metastatic disease setting. Merrimack has identified HRG mRNA expression as a potential resistance marker to endocrine therapies and is evaluating a combination of seribantumab + endocrine therapies to overcome the resistance exhibited by

HRG positive patients. Seribantumab blocks HRG binding to the ErbB3 receptor and has the potential to substantially increase PFS for patients with ER/PR positive, HER2 negative and HRG positive metastatic breast cancer, while maintaining an acceptable safety profile.

### 1.6.3. Rationale for Seribantumab Dose Selection

Pharmacokinetic (PK) analyses support using a fixed dosing regimen for seribantumab. Seribantumab will be administered at a fixed dose of 3 g on day 1 and 15 of each 28-day cycle.

Pharmacokinetics of seribantumab were evaluated using population pharmacokinetic analysis from 499 patients, comprising 4925 data points from the combined Phase 1 and Phase 2 studies. The pharmacokinetic data of seribantumab was described using a two-compartment model, with estimated parameters provided in Table 3. Covariate selection evaluated potential relationships between baseline covariates (sex, race, age, weight, intended-dose, and study/indication) with volume of distribution and clearance. The results indicated significant relationships between weight, sex, and clearance, with the final parameter estimates provided in Table 3. In particular, the model assumed a proportional relationship between the log of clearance (CL) and weight, and obtained an estimated proportionality constant of 0.203. In the presence of the relationship between weight and clearance, no significant relationship between volume and weight were observed.

To evaluate the benefit of weight-based dosing, a simulation study was conducted by comparing pharmacokinetics with weight-based and fixed dose regimens. The simulation results showed comparable variability between both fixed-dosing and weight-based dosing regimens, suggesting no benefits of the reduced PK variability with weight-based dosing (Figure 9). For example, a weight-based dosing of 20 mg/kg Q2W and a corresponding fixed dose of 1.5 g Q2W have comparable maximum, minimum, and average steady-state concentration levels and variability. The result can be explained because estimated proportionality between log of CL and weight is 0.203, and therefore, a weight-based regimen (which assumed a proportionally constant of one between log of CL and weight) would tend to overdose higher-weight patients.

To evaluate the optimization of seribantumab dosing regimens for improved compliance and simplicity, a simulation study was conducted to evaluate different dose intervals. The results showed the potential to optimize the dosing frequency to once every 2 weeks. A dose regimen of 3 g Q2W is predicted to have:

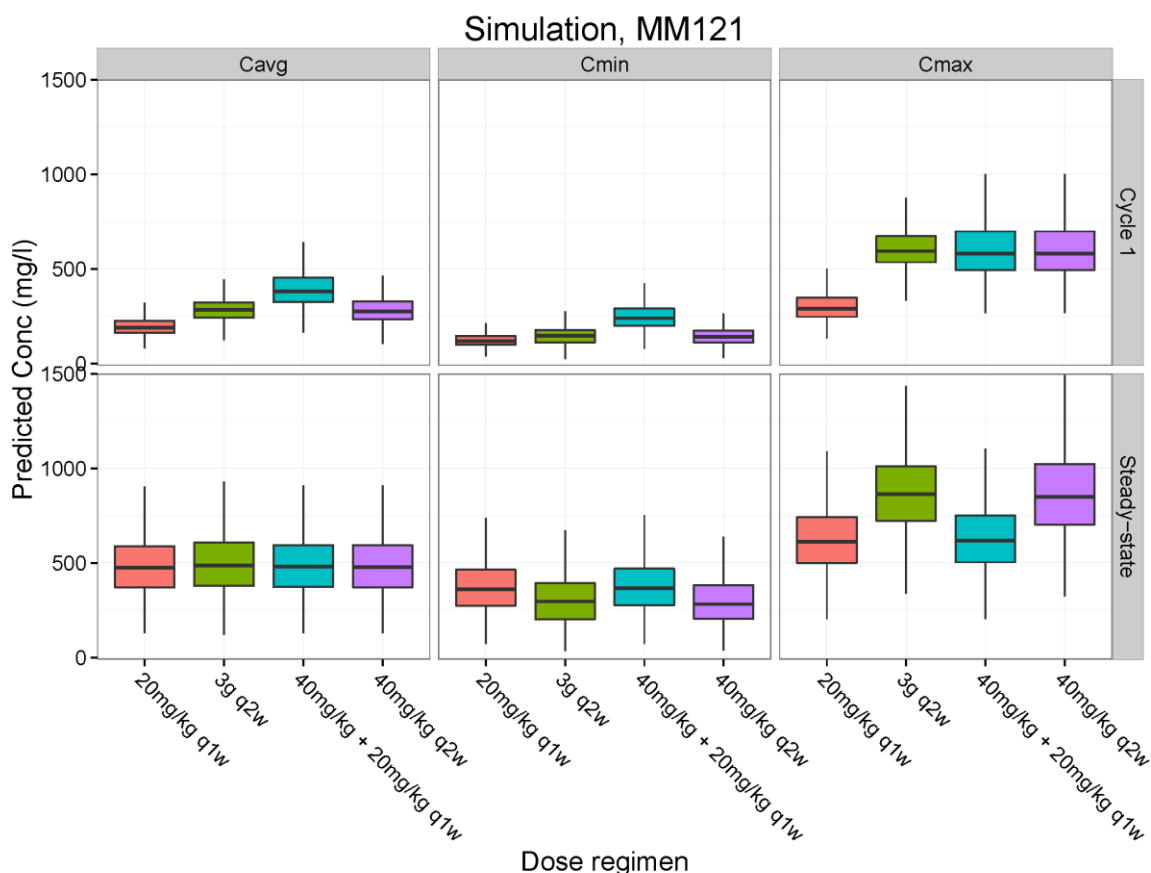
- A comparable maximum concentration ( $C_{\max}$ ) to 40 mg/kg Q2W (40 mg/kg was previously used as a loading dose for weight-based and weekly seribantumab dosing regimens);
- A comparable steady-state average concentration ( $C_{\text{avg}}$ ) to previous dose used in the previous Phase 2 study (40mg/kg + 20 mg/kg Q1W);
- A comparable minimum steady-state concentration to a dose regimen of 40mg/kg Q2W (the comparable weight-based dose with 3 Q2W).

Therefore, seribantumab dose regimen of 3 g Q2W has a potential to improve compliance, while maintaining the pharmacokinetic levels within the bounds of the exposures observed from previously studied seribantumab doses (40mg/kg + 20 mg/kg Q1W).

**Table 3: Final Parameter Estimates from Population PK Analysis of Seribantumab**

Parameters	(Estimated) Values
Number of patients	499
Fixed effects	
CL (L/wk)	3.15
V (L)	3.23
Q (L/wk)	2.92
V2 (L)	2.68
Random effects	
Omega CL (%)	36%
Cov CL and V (%)	27%
Omega V (%)	37%
Sigma	
Additive	25.18
Proportional	0.23
Covariate selection	
WT-CL	0.203
SEX-CL	0.255
WT-V	0.002

**Figure 11: Simulated Seribantumab Pharmacokinetics (Average concentration) by Weight-based and Fixed Dosing Regimens and by Dose and Intervals.**





## 2. Objectives

### 2.1. Primary Objective

The primary objective of this study is 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  $\geq 1+$ ).

### 2.2. Secondary Objectives

The secondary objectives of this study are as follows:

- To determine whether the combination of seribantumab plus fulvestrant is more effective than placebo plus fulvestrant in HRG positive patients (defined as HRG ISH score of  $\geq 1+$ ) 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

### 2.3. Exploratory Objectives

The exploratory objectives of this study are as follows:

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

## 3. Study Design

### 3.1. Overview of Study Design

This study is a multi-center, randomized, double-blind, placebo-controlled Phase 2 study of seribantumab in women with ER/PR positive, HER2 negative, locally advanced or metastatic breast cancer whose tumor expresses HRG as measured by RNA in-situ hybridization (RNA-ISH). The purpose of the study is to assess if the addition of seribantumab to fulvestrant is more effective than placebo plus fulvestrant in prolonging progression-free survival in this patient population.

Following signing informed consent and evaluation of initial eligibility criteria, all patients will provide a tissue sample (which meets the requirements for collection and processing as outlined in the study lab manual) for HRG testing. Descriptions of tissue types that are acceptable for testing are provided in Section 6.3.1. If adequate tissue is not available, patients should undergo a fresh tumor biopsy to obtain the adequate tissue required to perform HRG testing. For these procedures, investigators are asked to choose an easily accessible tumor lesion to minimize any possible risk associated with the collection of the tissue. As a general guideline, if the selected procedural location of the biopsy has an established serious complication rate of  $>2\%$  at the institution completing the procedure, this is considered a high risk procedure and should be avoided. Upon receipt of a tissue sample at the central lab, the investigational site will be informed of the results within 7 days. Patients with a positive HRG status, defined as HRG ISH



score of  $\geq 1+$ , will be eligible for randomization. Patients with tumors that show no staining for HRG (ISH score = 0) will not continue any further procedures for this study and will be considered screen failures. Minimal medical history for HRG negative patients will be collected.

Prior to receiving the first dose, all HRG positive patients that receive HRG results for eligibility based on testing of archived samples will also be asked to undergo a fresh research biopsy (either FNA or core needle) prior to first dose. An additional sample will not be requested from patients who underwent a fresh biopsy for eligibility testing. Once all screening procedures have been completed and eligibility for treatment randomization (including HRG positive ISH result) has been determined, the may randomize the patient. Patients will be randomized in a 1:1 ratio (experimental arm versus comparator arm) using an Interactive Web Response System (IWRS). Randomization will be stratified based on bone-only disease (yes, no), and geographic status (US, non-US).

Patients will be randomized to Arm A or Arm B:

**Arm A (Experimental Arm):**

- Seribantumab: fixed dose of 3000 mg IV on days 1 and 15 of each 28-day cycle
- Fulvestrant: 500 mg intramuscularly (IM) on days 1 and 15 of Cycle 1, and on Day 1 of each subsequent 28 day cycle

**Arm B (Comparator Arm):**

- Placebo: intravenously (IV) on days 1 and 15 of each 28-day cycle
- Fulvestrant: 500 mg IM on days 1 and 15 of Cycle 1, and on day 1 of each subsequent 28 day cycle

Treatment must start within 7 days following randomization. It is intended that patients will be treated until investigator-assessed disease progression or unacceptable toxicity, whichever comes first. Tumor assessments will be measured and recorded by the local radiologist every 8 weeks (+/- 5 days) from randomization using the RECIST guidelines (version 1.1). Tumor assessments will be performed every 8 weeks regardless of dose delays or dose interruptions, until investigator-assessed progressive disease. Patients who come off study treatment prior to disease progression, for reasons including patient or physician decision or unacceptable toxicity, will continue to undergo tumor assessments every 8 weeks ( $\pm 5$  days) until investigator assessed PD. Patients will be treated according to local assessment of tumor scans, and the primary analysis will be conducted based on investigator assessments.

All patients will have a follow-up visit scheduled 30 days ( $\pm 7$  days) after the last dose of study treatment, regardless of reason for treatment termination. Patients will not be allowed to cross over from placebo to seribantumab.

Survival follow up will be required for all patients every 2 months from the 30-day follow-up visit until death, loss to follow-up, withdrawal of consent, or study termination. After patients discontinue study treatment, subsequent anti-cancer therapies will be collected at the same time as survival follow-up.

An independent data monitoring committee (DMC) will be established to monitor emerging safety data and evaluate for trial efficacy. The DMC will regularly monitor safety data over the course of the study in accordance with the DMC Charter.

## 4. Study Population

The target population for this study is women who are candidates to receive single agent fulvestrant endocrine therapy for metastatic, ER/PR+ and HER2 negative breast cancer. Such patients shall not have received prior treatment with chemotherapy in the locally advanced or metastatic disease setting and must have failed prior systemic therapy with a CDK inhibitor, and have tumors that are positive for heregulin (HRG) mRNA as assessed by RNA-ISH testing. Patients cannot have received more than a total of two prior lines of therapy in the locally advanced or metastatic setting. There is no restriction on chemotherapy use in the neoadjuvant or adjuvant settings. The investigator or his/her designee must ensure that all patients meet the following inclusion and exclusion criteria before being enrolled in the study:

### 4.1. Inclusion Criteria

To be eligible for participation in the study, patients must meet the following criteria. Patients who are HRG negative do not need to complete screening procedures beyond HRG assessment:

- a) Histologically or cytologically confirmed ER+ and/or PR+ (with staining of  $\geq 1\%$  cells) breast cancer
- b) Confirmed postmenopausal status due to either surgical/natural menopause or ovarian suppression (initiated at least 28 days prior to Day 1 of Cycle 1) with a gonadotropin-releasing hormone (GnRH) agonist such as goserelin
- c) HER2 negative per ASCO/CAP guidelines
- d) A positive in-situ hybridization (ISH) test for heregulin with a score of  $\geq 1+$ , as determined by centralized testing of unstained tumor tissue
- e) Must have at least one lesion amenable to either core needle biopsy or fine needle aspiration
- f) Progressed following at least one but no more than two prior systemic therapies in the locally advanced or metastatic disease setting
  - Received prior CDK inhibitor based therapy for locally advanced or metastatic disease
- g) Documented progression of locally advanced or metastatic disease as defined by RECIST v1.1. *Exception:* patients with bone-only metastatic disease are eligible if they have at least 2 lytic lesions visible on a CT or MRI and have documented disease progression on prior therapy based on the appearance of new lesions.
  - Patients with bone-only lesions who have received radiation to those lesions must have documented progression following radiation therapy.
- h) Able to understand and sign an informed consent (or have a legal representative who is able to do so)
- i) ECOG Performance Score (PS) of 0 or 1
- j) Adequate bone marrow reserves as evidenced by:
  - ANC  $> 1500/\mu\text{l}$
  - Platelet count  $> 100,000/\mu\text{l}$ ; and
  - Hemoglobin  $> 9 \text{ g/dL}$
- k) Adequate hepatic function as evidenced by:
  - Serum total bilirubin  $\leq 1.5 \times \text{ULN}$  except for patients with Morbus Gilbert
  - Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and Alkaline Phosphatase  $\leq 2.5 \times \text{ULN}$  ( $\leq 5 \times \text{ULN}$  is acceptable if liver metastases are present,

and  $\leq 5 \times \text{ULN}$  of Alkaline Phosphatase is acceptable if bone metastases are present)

- l) Adequate renal function as evidenced by a serum creatinine  $\leq 1.5 \times \text{ULN}$
- m) Recovered from clinically significant effects of any prior surgery, radiotherapy, or other antineoplastic therapy.
- n) Patients may be treated with bone modifying agents such as bisphosphonates or receptor activator of nuclear factor kappa-B (RANK)-ligand agents (e.g. denosumab) per American Society of Clinical Oncology (ASCO) guidelines; whenever possible, patients requiring bone modifying agents should start treatment  $\geq 7$  days prior to study therapy and should continue the same agent throughout study unless clinically compelled to change
- o)  $\geq 18$  years of age
- p) Patients who have experienced a venous thromboembolic event within 60 days of signing the main consent form should have been treated with anti-coagulants for at least 7 days prior to beginning treatment and for the duration of treatment on this study.

#### 4.2. Exclusion Criteria

Patients must meet all the inclusion criteria listed above and none of the following exclusion criteria:

- a) Prior treatment with an anti-ErbB3 antibody
- b) Prior treatment with a chemotherapy in the locally advanced or metastatic disease setting
- c) Patients cannot have received prior treatment with fulvestrant or other SERDs in the locally advanced or metastatic setting
- d) Uncontrolled CNS disease or presence of leptomeningeal disease
- e) Inflammatory breast cancer
- f) History of another active malignancy that required systemic therapy in the last 2 years. Patients with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible
- g) Active infection, or an unexplained fever  $> 38.5^{\circ}\text{C}$  during screening visits or on the first scheduled day of dosing, which in the investigator's opinion might compromise the patient's participation in the trial or affect the study outcome. At the discretion of the investigator, patients with tumor fever may be enrolled
- h) Known hypersensitivity to any of the components of seribantumab, fulvestrant, or who have had hypersensitivity reactions to fully human monoclonal antibodies
- i) Received other recent antitumor therapy including:
  - Investigational therapy administered within the 28 days or 5 half-lives, whichever is shorter, prior to the first scheduled day of dosing in this study
  - Radiation or other standard systemic therapy within 14 days prior to the first scheduled dose in this study, including, in addition (if necessary), the timeframe for resolution of any actual or anticipated toxicities from such radiation
- j) NYHA Class III or IV congestive heart failure
- k) Patients with a significant history of cardiac disease (i.e. uncontrolled blood pressure, unstable angina, myocardial infarction within 1 year or ventricular arrhythmias requiring medication) are also excluded

- l) Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals; or active human immunodeficiency virus (HIV) infection, active hepatitis B infection or active hepatitis C infection
- m) Any other medical condition deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, interfere with a patient's ability to cooperate and participate in the study, or interfere with the interpretation of the results

#### **4.3. Assessing Heregulin Status in Breast Cancer Specimens**

This study will only enroll patients with HRG positive tumors (defined as tumors with a HRG RNA-ISH score of  $\geq 1+$ ). Patients presenting with HRG negative tumors (HRG ISH score of 0) will not undergo any additional study procedures and will be considered screen failures; however, some minimal medical history information will be collected. A patient's tumor HRG status will be assessed at a central CLIA certified lab using a qualified RNA in situ hybridization (ISH) assay.

##### **4.3.1. Description of HRG RNA-ISH Assay**

RNA-ISH is a test in which oligonucleotide target probes are hybridized to the RNA in formalin-fixed, paraffin-embedded (FFPE) tissue samples. The signal on the target RNA molecule is detected by using a chromogenic substrate reaction. This approach enables mRNA molecules to be visualized and scored by pathologists in a manner similar to a standard immunohistochemistry (IHC) assay.

##### **4.3.2. Implementation of HRG RNA-ISH Testing**

The HRG RNA-ISH assay can be used to measure mRNA expression on tissue slides obtained from formalin-fixed paraffin embedded archived blocks, core biopsies or fine needle aspirates; therefore, any of these methods of collection is acceptable for testing. Formalin-fixed clinical trial specimens will be submitted directly by clinical sites to the designated CLIA certified central lab. Full details regarding collection, processing and shipment of samples are outlined within the study lab manual.

The central lab will process the samples and provide the stained slides to a trained pathologist to assess tumor content and percentage of tumor cells expressing HRG mRNA. The pathologist will assign scores of 0, 1+, 2+, or 3+ based on HRG mRNA staining. Samples scored at  $\geq 1+$  will be considered HRG positive, and samples scored at 0 will be considered HRG negative. This result will be communicated back to the investigative site within 7 days of sample receipt at the central lab.

#### **4.4. Patient Discontinuation**

A patient may withdraw from the study at any time and for any reason. It is intended that patients will be treated until investigator-determined progressive disease (radiologic or clinical deterioration) or unacceptable toxicity. Some possible reasons for withdrawal from treatment include, but are not limited to the following:

- Progressive neoplastic disease per RECIST v1.1
- Clinical deterioration
- Adverse event, including treatment being withheld for 21 consecutive days without resolution of toxicities to grade 1 or baseline value

- Protocol violation / non-compliance
- Withdrawal of consent
- Investigator or sponsor decision
- Patient is lost to follow-up

When a patient is discontinued from treatment for any reason, they are to undergo the assessments in the End of Treatment visit within 30 days of the last dose. All patients who discontinue treatment as a result of an adverse event must be followed until resolution or stabilization of the adverse event. At the time a patient withdraws from study treatment, an attempt should be made to determine the reason(s) for discontinuation. The patient will continue to be followed for survival information every 2 months after completion of the End of Treatment visit. All patients, including patients who discontinue treatment for reasons other than progressive disease per RECIST 1.1, should undergo a scan to assess disease status at the time of treatment discontinuation, and again 8 weeks following treatment termination.

If a patient does not return to the clinic for the end of treatment visit or is not reached for overall survival follow-up, at least 3 documented attempts, including one via certified mail, should be made to contact the patient. If there is no response to these requests, the date of death should be captured from public records.

## **5. Study Treatment**

### **5.1. Method of Assigning Patients to Treatment Groups**

If a patient is determined to be HRG positive, investigators will determine whether all other study enrollment criteria have been fulfilled. Upon completion of screening assessments, eligible, patients will be randomized 1:1 to the treatment or control arm using an Interactive Web Response System (IWRS). Randomization will be stratified based on bone-only disease (yes, no) and geographic status (US, non-US).

### **5.2. Seribantumab**

#### **5.2.1. Seribantumab Formulation, Packaging, and Labeling**

Seribantumab is supplied for IV administration as a sterile, colorless liquid at 25 mg/mL. It is packaged in sterile, single-use, clear borosilicate Type 1 glass vials that are closed with a coated rubber stopper and flip-off cap with flange.

Multiple vials of seribantumab will be packaged in a cardboard container. The individual vials, as well as the outside of the cardboard container, will be labeled in accordance with regulatory requirements and in compliance with country-specific guidelines. Additional details are provided in the study pharmacy binder.

#### **5.2.2. Seribantumab Product Storage and Stability**

Seribantumab Drug Product must be stored refrigerated (2-8°C) with protection from light. Light protection is not required during preparation or infusion. Seribantumab must not be frozen.

Based on available stability data, the concentrate for solution for infusion is stable for at least 36 months when stored according to conditions specified in the clinical supply label. Continued stability data are being generated, and longer stability may be available during the course of the

study. The date of expiration will be noted on the drug label, or via other pharmacy notifications as required by local regulation. Seribantumab should not be used beyond the date of expiration.

### **5.2.3. Seribantumab Dosage, Preparation, and Administration**

Seribantumab should be administered as an IV infusion at a fixed dose of 3000 mg on day 1 and day 15 of each 28-day cycle.

Administration of seribantumab will require multiple vials, all of which should come from the same lot number. Seribantumab should be brought to room temperature prior to mixing with saline. Vials of seribantumab should not be shaken. The appropriate quantity of study drug will be removed from the vial, diluted with 0.9% normal saline to a final volume of 250 ml and administered over 60 minutes ( $\pm 15$  minutes) for all infusions in the absence of infusion reactions, using a low protein binding 0.22 micrometer in-line filter. The equivalent amount of saline should be removed from the infusion bag to fill with seribantumab to 250 ml. The line should be flushed before and after the study drug infusion. Study drug should not be administered as a bolus or a push.

### **5.2.4. Management of Infusion Reactions to Seribantumab**

Like other IV infusions, seribantumab administration may be associated with infusion related reactions (IRRs). Infusion related reactions will be defined according to the National Cancer Institute CTCAE (Version 4.03) definition of an allergic reaction/infusion reaction and anaphylaxis. In past clinical studies, IRRs with seribantumab have been rare with  $< 1\%$  of patients reporting an IRR, of which all were Grade 1 or 2. Study site policies or the following treatment guidelines shall be used for the management of infusion reactions.

#### Grade 1

- Slow infusion rate by 50%
- Monitor patient every 15 minutes for worsening of condition

#### Grade 2

- Stop infusion
- Administer diphenhydramine hydrochloride 50 mg IV, acetaminophen 500-650 mg orally or IV, and oxygen
- Resume infusion at 50% of the prior rate once infusion reaction has resolved
- Monitor patient every 15 minutes for worsening of condition
- For all subsequent infusions, pre-medicate with dexamethasone 10 mg orally or IV

#### Grade 3

- Stop infusion and disconnect infusion tubing from patient
- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, bronchodilators for bronchospasm, and other medications or oxygen as medically necessary
- No further treatment with seribantumab will be permitted

#### Grade 4

- Stop the infusion and disconnect infusion tubing from patient
- Administer epinephrine, bronchodilators or oxygen as indicated for bronchospasm

- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV
- Consider hospital admission for observation
- No further treatment with seribantumab will be permitted

For patients who experience a Grade 1 or Grade 2 infusion reaction, at the discretion of the investigator, future infusions may be administered at a reduced rate (over 90 minutes).

For patients who experience a second Grade 1 or 2 infusion reaction, administer dexamethasone 10 mg IV. All subsequent infusions should be pre-medicated with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 500-650 mg orally.

For patients who experience a Grade 3 or 4 infusion reaction, an anti-seribantumab antibody titer will be taken as close to the onset of the infusion reaction as possible for any patient experiencing an infusion reaction to seribantumab. Anti-seribantumab antibody titer should also be obtained at the resolution of the event and 28 days (+/- 2 days) following the event.

### **5.2.5. Management of Toxicity Related to Seribantumab**

In the event that a patient experiences a toxicity  $\geq$  Grade 3 that is not an IRR and is possibly, probably or definitively related to seribantumab treatment, and not related to fulvestrant, it is at the investigator's discretion to hold dosing or discontinue treatment with seribantumab. Prior to holding the dose or discontinuing treatment, the investigator must notify the sponsor and Medical Monitor.

In the event that seribantumab treatment has been held for 28 consecutive days, the patient should be discontinued. No dose reductions for seribantumab are permitted.

#### **5.2.5.1. Potential Toxicities with the Combination of Seribantumab and Fulvestrant**

In addition to the established toxicities of fulvestrant, it is expected that the addition of seribantumab to fulvestrant may lead to an increased frequency of low grade diarrhea, rash, alopecia, stomatitis, hypokalemia and hypomagnesaemia. A slight increase in grade 3 diarrhea and/or hypokalemia may be observed, as well, in the combination setting. In previous studies, these events were generally well controlled with symptomatic treatments per institutional standards.

Pulmonary embolisms, which exist as an identified risk for chemotherapies ([Karavasilis et al., 2014](#); [Kellokumpu-Lehtinen et al., 2012](#); [Matulonis et al., 2008](#); [Reck et al., 2014](#)) have also been described as an adverse event of special interest (AESI) for ErbB-pathway related inhibitors, including seribantumab when administered in combination with paclitaxel. Increased frequencies were observed in combination of seribantumab with paclitaxel in two completed randomized studies in neo-adjuvant breast cancer (4 (3.1%) on the treatment arm vs. 0 (0%) on the control arm) and platinum-resistant ovarian cancer (6 (4.3%) on the treatment arm vs. 1 (1.3%) on the control arm). There was no general increase in venous thromboembolic events reported for these two studies. Pulmonary embolisms may be observed at a higher frequency with the combination of seribantumab and endocrine therapies. No increases in the frequency of pulmonary embolisms or other venous thromboembolic complications were observed in randomized studies with seribantumab in combination with exemestane in metastatic breast cancer.

Patients who have experienced a venous thromboembolic event within 60 days of signing the main consent form for this study should have been treated with anti-coagulants for at least 7 days prior to beginning treatment and for the duration of treatment on this study.

### **5.3. Fulvestrant**

Fulvestrant (trade name: Faslodex®) is an estrogen receptor (ER) antagonist that binds to the estrogen receptor in order to downregulate the ER protein in human breast cancer cells.

For managing patients receiving fulvestrant, investigators can use institutional guidelines, the fulvestrant package insert, or the following, which has been obtained from the Faslodex® US package insert ([AstraZeneca, 2012](#)).

#### **5.3.1. Fulvestrant Formulation, Packaging, Labeling, and Storage**

Please refer to the fulvestrant package insert located in the pharmacy binder for specific information on the fulvestrant formulation.

Fulvestrant will be supplied by the Sponsor and labeled for investigational use only according to local regulations. Fulvestrant will be supplied as two 5-mL clear neutral glass barrels, each containing 250 mg/5 mL of fulvestrant solution for intramuscular injection and fitted with a tamper evident closure. The solution for injection is a clear, colorless to yellow, viscous liquid.

Fulvestrant should be stored at refrigerated (2-8 °C). It should be stored protected from light and in the original packaging until the time of use.

#### **5.3.2. Fulvestrant Dosage and Administration**

The approved dose of fulvestrant is 500 mg administered intramuscularly into the buttocks. The injection should be as two 5 mL injections and should be administered slowly (1-2 minutes per injection). Injections should be given on days 1 and 15 of Cycle 1, and on day 1 of each subsequent 28 day cycle.

Technique for administration of the injection is outlined in the package insert. Because fulvestrant is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use.

#### **5.3.3. Fulvestrant Dose Modifications**

In the event that an Investigator believes a dose modification is required for fulvestrant, the Sponsor and Medical Monitor should be contacted. The Investigator should use the local package insert for current dose modification guidelines for fulvestrant.

#### **5.3.4. Potential Toxicities with Fulvestrant**

Because fulvestrant is given intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use.

Investigators should refer to the current fulvestrant package insert for information regarding potential interactions and toxicities.

In a clinical trial of fulvestrant given at 500 mg in advanced breast cancer as described in the current US fulvestrant package insert ([AstraZeneca, 2012](#)), the most frequently reported adverse events include: injection site pain (11.6%), nausea (9.7%), and bone pain (9.4%). Additional adverse events reported in  $\geq 5\%$  of patients include: arthralgia (8.0%), headache (7.8%), back



pain (7.5%), fatigue (7.5%), extremity pain (6.9%), hot flashes (6.6%), vomiting (6.1%), anorexia (6.1%), asthenia (5.8%), musculoskeletal pain (5.5%), cough (5.3%), and constipation (5.0%).

Safety information for fulvestrant can be updated at any time by the original manufacturer. Merrimack Pharmaceuticals does not own rights to or make updates to the overall safety information distributed for fulvestrant. For this reason, Investigators should refer to the most current package insert for fulvestrant for any changes in safety information.

#### **5.4. Rules for Dose Omissions and Modified Treatment Schedules**

It is intended that seribantumab and fulvestrant dosing occur on schedule per the protocol. In the event that dosing of any study drug has been held for 28 consecutive days and the investigator does not wish to continue dosing, the patient should be discontinued from treatment.

Dose modifications of seribantumab are not allowed. Any dose modifications to fulvestrant should be performed in line with the local package insert, and should be discussed and approved by the Sponsor prior to implementation.

#### **5.5. Concomitant and Prohibited Therapies**

All intercurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the investigator according to acceptable local standards of medical care. Patients should receive analgesics, antiemetics, antibiotics, anti-pyretics, GCSF, peg-GCSF, and blood products as necessary. All concomitant medications, including transfusions of blood products, will be recorded on the appropriate page of the case report form. Concomitant therapy (non-investigational products) includes any prescription medication, over-the-counter preparation, herbal therapy, or radiotherapy used by a patient between the 28 days preceding randomization and the study treatment discontinuation visit. After the End of Treatment Visit, only anti-cancer therapies will be collected.

The following therapies are not permitted while on study treatment:

- Other anti-neoplastic therapy, including cytotoxics, targeted agents, endocrine therapy or other antibodies (patients who have been on GnRH analogues for more than 90 days prior to study entry may continue on these while on study)
- Radiotherapy (patients who require a short course of palliative radiotherapy may continue on the study treatment after discussion between the investigator and sponsor)
- Any other investigational therapy

#### **5.6. Accountability of Study Drug**

The investigator and investigational site staff are responsible for maintaining an accurate inventory and accounting of study drug. A record of all vials and tablets of study drug received and administered will be maintained on an investigational drug inventory form provided by the Sponsor or an equivalent drug inventory form. The following information will be recorded:

- Date and quantity of study drug received
- Date and quantity of study drug dispensed from the pharmacy per patient
- Date and quantity of study drug administered to each patient
- Date and quantity of study drug destroyed (if prepared and dispensed, but not administered for any reason, the study drug may not be returned to inventory)

- Date and quantity of study drug returned to sponsor, if applicable

Each shipment of study drug will contain an invoice describing the amount of drug shipped to the investigational site. The information on the invoice will be verified against the actual amount of drug received, after which the investigator or the investigator's designee will place the invoice in the investigator's file.

The sponsor's monitor will reconcile the information on the investigational drug inventory form with the actual amount of study drug remaining at each site on a routine basis. At the conclusion of the study, the monitor will either package and ship all unused vials of study drug back to Sponsor for destruction or document the destruction, in accordance with local regulations and institutional policy. Following use, empty vials of study drug may be destroyed according to local regulatory and environmental requirements. A record of any such destruction will be placed in the investigator's file.



## 6. Schedule of Assessment

### 6.1. Schedule of Assessments: Heregulin Positive Patients

Procedure	Screening Visit	Cycle 1 <sup>6</sup>				Cycle 2 <sup>6</sup>				Additional Cycles <sup>6</sup>				Every 8 weeks from first dose <sup>4</sup>	30 Day Follow-Up <sup>14</sup>	Every 2 months from FU Visit
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4			
Informed Consent	X															
HRG Testing	X <sup>1</sup>															
Tumor Biopsy <sup>11</sup>	X															
Medical history	X <sup>1</sup>															
Demographics	X <sup>1</sup>															
Vital signs	X <sup>2</sup>	X		X		X		X		X		X			X	
ECOG PS	X <sup>2</sup>	X				X				X					X	
CBC	X <sup>2</sup>	X		X		X		X		X		X			X	
Serum chemistry	X <sup>2</sup>	X		X		X		X		X		X			X	
Coagulation profile	X <sup>2</sup>	X				X				X					X	
Pregnancy test	X <sup>2</sup>														X	
ECG	X <sup>1,3</sup>	X <sup>16</sup>				X <sup>16</sup>				X <sup>16</sup>						
ECHO/MUGA <sup>19</sup>	X <sup>1</sup>													X	X <sup>20</sup>	
Archived tumor, if available	X															
Fresh tumor biopsy	X <sup>11</sup>															
Serum for seribantumab PK <sup>7</sup>		X <sup>7a</sup>		X <sup>7b</sup>		X <sup>7b</sup>		X <sup>7b</sup>								
Serum for Ig <sup>8,9</sup>		X				X				X					X	
Serum for biomarkers <sup>14</sup>		X				X				X						
Plasma for ESR1 testing		X <sup>21</sup>													X	
Plasma for fulvestrant PK		X <sup>12</sup>		X <sup>12</sup>		X <sup>12</sup>		X <sup>12</sup>								
Concomitant meds	X <sup>1</sup>	X		X		X		X		X		X			X	
Seribantumab dosing		X		X		X		X		X		X				
Fulvestrant dosing		X		X		X				X						
SAE/AE assessment and reporting <sup>17</sup>	Continuous monitoring															
Hospitalization reporting <sup>18</sup>		X		X		X		X		X		X			X	X
Disease evaluation <sup>10</sup>	X <sup>1</sup>													X <sup>5</sup>	X	
Overall Survival Reporting																X <sup>15</sup>

- 
- <sup>1</sup> Procedures to be completed within 28 days of signing the **main** informed consent form
- <sup>2</sup> Procedures to be completed within 7 days of first dose of Seribantumab
- <sup>3</sup> Two independent readings at least 5 minutes apart
- <sup>4</sup> Evaluations may be performed  $\pm$  1 week from the scheduled date of visit
- <sup>5</sup> Any patient that comes off treatment for reasons other than progressive disease, will have a scan to assess disease status at the time of treatment discontinuation and additional scans every 8 weeks (+/- 1 week) until investigator-assessed PD
- <sup>6</sup> All procedures should occur  $\pm$ 2 calendar days from scheduled date of visit
- <sup>7</sup> Seribantumab PK: all patients; in relation to seribantumab infusion
- <sup>a</sup> C1W1: immediately after the end of the Seribantumab infusion (+15 mins)
- <sup>b</sup> C1W3, C2W1, C2W3: pre-dose
- <sup>8</sup> Immunogenicity samples should be collected for all patients prior to dosing.
- <sup>9</sup> In the event a patient experiences an infusion reaction at any point in the study, an anti-Seribantumab antibody assay will be taken within 24 hours of the event, in addition to the scheduled time-points. For patients who experience a Grade 3 or 4 infusion reaction to Seribantumab, an anti-Seribantumab antibody titer will be taken as close to the onset of the infusion reaction as possible, at the resolution of the event and 28 days (+/- 2 days) following the event.
- <sup>10</sup> Disease evaluation per RECIST version 1.1.
- <sup>11</sup> Tumor sample is to be collected for all HRG positive patients that receive HRG results for eligibility based on testing of archived samples. An additional sample is not required for patients who underwent a fresh biopsy for eligibility testing.
- <sup>12</sup> Fulvestrant PK: all patients: prior to seribantumab injection
- <sup>13</sup> Serum for biomarkers should be collected pre-infusion on week 1 of each cycle for all patients
- <sup>14</sup> End of treatment (30-day Follow-up) visit should be completed within 30 days of the last dose of study drug
- <sup>15</sup> Should patients refuse or drop out of survival follow-up, attempts should be made to obtain any death information available via public records.
- <sup>16</sup> One reading prior to infusion with seribantumab.
- <sup>17</sup> AE/SAE collection to be included. S/AE assessment and reporting will proceed as outlined in Sections [9.2](#) and [9.3](#)
- <sup>18</sup> All patient hospitalizations and/or hospital visits should be collected, whether or not associated with an adverse event.
- <sup>19</sup> In addition to the timepoints noted, MUGA or Echocardiogram should be performed post-screening for any study patient who develops symptoms consistent with new onset of congestive heart failure.
- <sup>20</sup> Unless performed within the last 4 weeks as part of assessments in the previous cycle
- <sup>21</sup> Sample to be collected prior to any study treatment.

## 6.2. Schedule of Assessments: HRG Negative Patients

Procedure	Screening Visit
Informed consent <sup>1</sup>	X
SAE assessment and reporting <sup>2</sup>	X
Cancer Diagnosis History <sup>3</sup>	X
Prior Anti-Cancer Therapies <sup>3</sup>	X
Prior Radiotherapies <sup>3</sup>	X

<sup>1</sup> To be completed prior to any study-related procedures.

<sup>2</sup> Any serious adverse events considered by the Investigator to be directly related to screening procedures (i.e. related to screening biopsy) should be collected and reported from the time of informed consent up to receipt of HRG results.

<sup>3</sup> Minimal medical history will be collected from all HRG negative patients.

## 6.3. Screening and Baseline Visit

All procedures for screening and baseline are outlined in Section 6.1. The window for screening procedures begins after signing the main consent form. For further descriptions of the clinical and laboratory assessments required, please refer to Section 7 and 8 respectively.

### 6.3.1. RNA-ISH Heregulin Testing

All patients must submit a tissue sample for RNA-ISH testing of heregulin levels as soon as possible following signing the informed consent form, as this will determine patient eligibility for treatment randomization and subsequent screening procedures. The HRG RNA-ISH assay can be used to measure mRNA expression on tissue slides obtained from formalin-fixed paraffin embedded archived blocks, core biopsies or fine needle aspirates; therefore, any of these methods of collection is acceptable for testing.

If archive tissue is being used for eligibility testing, the most recent sample available should be submitted. Heregulin testing can be performed on tissue obtained at the following times:

- At the time of initial diagnosis
- At the time of metastatic diagnosis
- or on tissue obtained from a fresh tumor biopsy.

If collection of fresh tissue is required in order to provide adequate tissue for testing, attempts should be made to acquire tissue from a tumor in a non-significant risk location, as determined by the investigator. As a general guideline, if the selected procedural location of the core needle biopsy or FNA has an established serious complication rate of >2% at the institution completing the procedure, this is considered a high risk procedure and should be avoided. Primary tumor samples and samples obtained from metastatic sites are both acceptable.

Preparation of samples for HRG testing should be conducted in accordance with the laboratory manual. Specific procedures for the collection and processing of bone biopsies are provided in the manual.

Samples will be processed and analyzed at a central facility where they are scored by a pathologist as specified in the lab manual with a turnaround time of no longer than 7 days from date of receipt by the central lab. Any patient who scores positive (a score of  $\geq 1+$ ) for HRG mRNA will be eligible for the study and should continue with screening procedures.

### **6.3.2. Heregulin Negative Patients**

Any patient whose tissue is negative (score of 0) for heregulin as determined by the RNA-ISH test will be considered a screen failure. Minimal medical history for HRG negative patients will be collected as outlined in Section 6.2.

### **6.4. On-Study Visits**

Patients who are confirmed to meet all inclusion and exclusion criteria will be randomized via an IWRS. Randomization must occur within 7 days of first dose (cycle 1 day 1).

All on-study procedures and assessments are outlined in Section 6.1. During the treatment period, a window of  $\pm 2$  days will apply to all visits, unless otherwise stated.

### **6.5. End of Treatment Visit**

When it is decided that a patient will stop receiving treatment on this study, an End of Treatment visit must be completed within 30 days of last dose of study drug. All End of Treatment procedures and assessments are outlined in Section 6.1.

### **6.6. Survival Follow-up**

Survival data will be collected via telephone or clinic visits every 2 months ( $\pm 10$  days) from the date of the 30-day follow-up visit until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor. In addition, any new anti-cancer therapies and procedures should be collected and documented. All survival information will be captured using the electronic data capture (EDC) system. Should patients refuse or drop out of survival follow-up, attempts should be made to obtain any death information via public records whenever possible.

## **7. Clinical Procedures and Assessments**

All following clinical procedures should be performed in accordance with the schedule of assessments outline in Section 6.1.

### **7.1. Medical History and Demographics**

Demographic information including age, date of birth, race, ethnicity and gender will be collected.

A medical history will be collected including all pertinent prior medical conditions, surgeries or other medical procedures, allergies, and concomitant medications.

### **7.2. Adverse Event and Hospitalization Assessment Reporting**

Investigators should complete all routine and standard of care assessments to evaluate for toxicity and symptoms of drug-induced adverse events. This may include, but is not limited to, verbal reports from the patient and/or caregiver, physical examination and laboratory findings. Adverse events should be reported throughout the course of the study beginning at the time of signing the main study informed consent form, until the study termination visit, and followed through to resolution as detailed in Section 9.

Adverse events and serious adverse events should not be reported for patients that only sign the biomarker informed consent form unless the event is considered by the investigator to be directly related to a study procedure (i.e. tumor biopsy for heregulin testing).

In addition, information on patient hospitalizations and/or unscheduled hospital visits should also be collected in the eCRF, whether or not associated with an adverse event.

### **7.3. Vital Signs**

Vital signs should include height (screening only), weight, resting blood pressure, pulse, respiratory rate, and temperature.

### **7.4. Performance Status Assessment**

The Eastern Cooperative Oncology Group (ECOG) performance status (PS) will be obtained by the PI or his/her designee by questioning the patient about their functional capabilities.

### **7.5. Electrocardiogram (ECG)**

A 12-lead electrocardiogram (ECG) will include a description of the cardiac rate, rhythm, interval durations, and an overall impression. QTc should be calculated using the Fridericia method (QTcF). ECGs will be performed for all patients at screening to rule out clinically significant abnormalities. For randomized patients, ECGs will be performed on week 1 of each cycle prior to dosing with seribantumab.

### **7.6. Echocardiogram or Multiple Gated Acquisition Scan**

An echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) will be performed to determine ejection fraction. The same procedure (ECHO or MUGA) performed during screening to determine the ejection fraction should be employed at subsequent visits. In addition to the required timepoints, ECHO or MUGA should be performed post-screening at any time for any study patient who develops symptoms consistent with new onset of congestive heart failure.

### **7.7. Disease Evaluation**

Tumor response will be evaluated by the local radiologist according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 ([Eisenhauer et al., 2009](#)) to establish disease progression by CT or MRI. In addition, other radiographic or scintigraphic procedures (such as radionuclide bone scans), as deemed appropriate by the investigator, will be performed to assess sites of neoplastic involvement. The same method of assessment must be used throughout the study. Please refer to image acquisition guidelines for the requirements for image collection and scanner qualification. Investigators should choose target and non-target lesions in accordance with RECIST v1.1 guidelines. Follow-up measurements and overall response should also be in accordance with these guidelines. To be assigned a status of confirmed partial response (PR) or complete response (CR), changes in tumor measurements must be confirmed by repeated assessments that should be performed  $\geq 30$  days after the criteria for response are first met.

Disease should be assessed every 8 weeks ( $\pm 5$  days) from randomization regardless of treatment schedule until investigator-assessed progression. In cases where there is a suspicion of disease progression prior to the next scheduled scan, an unscheduled assessment should take place. All patients who come off study treatment prior to disease progression for reasons including patient or physician decision or unacceptable toxicity will continue to undergo tumor assessments every 8 weeks ( $\pm 5$  days) until investigator-assessed progression of disease.

## 8. Laboratory Procedures and Assessments

### 8.1. Complete Blood Count (CBC)

The CBC will include the following: hemoglobin, hematocrit, platelet count, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils and other cells).

### 8.2. Coagulation Profile

A coagulation profile will include activated partial thromboplastin time (aPTT), prothrombin time (PT), and an international normalized ratio (INR).

### 8.3. Serum Chemistry

Serum chemistry will include electrolytes (sodium, potassium, chloride and bicarbonate), BUN, serum creatinine, glucose, bilirubin, AST, ALT, alkaline phosphatase, LDH, uric acid, total protein, albumin, calcium, magnesium and phosphate.

### 8.4. Urine or Serum Pregnancy Test

A urine or serum pregnancy test will be obtained for all females of childbearing potential. Exempt female patients will include those who have undergone a bilateral oophorectomy or hysterectomy, or those who are menopausal (defined as absence of a menstrual cycle for at least 12 consecutive months). The reason for exemption should be recorded in the medical history.

### 8.5. Pharmacokinetic Testing

#### 8.5.1. Seribantumab PK Samples

Blood samples will be collected from all patients to determine the levels of monoclonal antibodies that comprise seribantumab. The serum PK analysis will be performed post-dose on Cycle 1, Week 1, and pre-dose for all subsequent seribantumab infusions until the completion of Cycle 2, as outlined in [Table 4](#). Approximately 5 mL of blood will be collected. The real time of blood collection must be documented in the respective eCRF. A laboratory manual will be provided with instructions for collecting, processing, and shipping the samples.

PK samples should be collected at the following time-points relative to the seribantumab infusion:

**Table 4: Seribantumab PK Collection Timepoints**

Seribantumab PK Sample	Pre-infusion	Post-infusion
Cycle 1, Week 1		X
Cycle 1, Week 3	X	
Cycle 2, Week 1	X	
Cycle 2, Week 3	X	

#### 8.5.2. Fulvestrant PK samples

To determine the levels of fulvestrant, blood samples will be collected for all patients prior to the seribantumab dose on Cycle 1, Week 1, Cycle 1, Week 3, Cycle 2, Week 1, and Cycle 2, Week 3.

Approximately 5 mL of blood will be collected. The real time of blood collection must be documented in the respective eCRF. A laboratory manual will be provided with instructions for collecting, processing, and shipping the samples.



## **8.6. Anti-Seribantumab Immunogenicity**

Serum samples will be collected to determine the presence of an immunologic reaction to seribantumab (i.e. human anti-human antibodies; HAHA). A laboratory manual will be provided with instructions for collecting, processing, and shipping these samples.

## **8.7. Biomarker Samples**

Biomarker data will be explored from collected tissue and serum samples to assess potential associations with tumor response. To help further understand the biological phenotype of heregulin-positive ER/PR+ and HER2 negative breast cancer, these samples will be used to assess the mRNA and/or protein for clinically relevant biomarkers for breast cancer, including ErbB receptors, cMET, IGF-1R, and FGF receptor tyrosine kinases and their respective ligands (ErbB ligands, HGF, IGFs and FGFs). Efficacy outcomes considered for pre-specified mechanistic biomarker analysis will include OS, PFS, and ORR.

### **8.7.1. Tissue for HRG eligibility assessment**

The most recent available tumor tissue available from anytime between diagnosis and signing consent for this trial can be used for HRG testing. If no tissue is available, patients can undergo a fresh tissue biopsy, (either a CNB or FNA) to determine eligibility and are also asked to submit a second pass/ core or second aspirate for research purposes if possible. Directions for processing and shipping the tissue sample for heregulin testing can be found in the laboratory manual.

### **8.7.2. Tumor Biopsy**

Prior to receiving the first dose of study drug, all HRG positive patients should provide one fresh tumor biopsy for research purposes. This biopsy will be used to confirm HRG status, and samples will be used to conduct exploratory studies to further characterize and correlate possible biomarkers that may help to predict or evaluate response to seribantumab. Patients who undergo a fresh tumor sample for eligibility testing do not need to provide an additional sample.

### **8.7.3. Serum Samples**

Serum samples will be collected at time points described in Section 6.1. Serum will be collected from all patients. The samples will be used to conduct exploratory studies to further characterize and correlate possible biomarkers that may help to predict or evaluate response to seribantumab. In the event that there is remaining sample available after conducting these analyses, it will be stored and used by the Sponsor for future biomarker analysis. At the time of informed consent, patients will be able to refuse storage of these remaining samples. Directions for processing and shipping the samples can be found in the laboratory manual.

### **8.7.4. ESR1 Testing**

Plasma samples will be collected at time points described in Section 6.1 from all patients. These samples will be used to test for the ESR1 mutation in order to further characterize and correlate whether these mutations may help to predict or evaluate response to seribantumab. Directions for processing and shipping these samples can be found in the laboratory manual.

### **8.7.5. Archived Tumor Samples**

If available, formalin-fixed paraffin embedded tumor samples (either a tumor block or freshly cut slides) obtained at the time of diagnosis will be collected to compare a patients HRG status with

the screening tissue sample if different, for example, a fresh biopsy of a metastatic lesion. Directions and requirements for processing and shipping the archived tumor samples can be found in the laboratory manual.

## **9. Adverse Event and Hospitalization Reporting**

### **9.1. Definitions**

#### **9.1.1. Adverse Events**

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, including abnormal laboratory findings, symptoms, or diseases temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

#### **9.1.2. Serious Adverse Event**

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization (Exception: hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an adverse event. NOTE: Complications that occur during hospitalization are adverse events and if a complication prolongs hospitalization, then the event is serious);
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

While the term “severe” is often used to describe the intensity (severity) of an event, the event itself may be of relatively minor significance (such as a severe headache). This is not the same as “serious”, which is based on a patient/event outcome or action criteria usually associated with events that pose a risk to a patient’s life or functioning.

#### **9.1.2.1. Progressive Disease**

Because of the natural history of metastatic breast cancer, the vast majority of patients will progress on treatment due to their underlying condition, resulting in hospitalization, appropriate medical care or death. Therefore, progression of underlying malignancy will not be recorded and reported as an adverse event or serious adverse event. In the event that the investigator is unsure

whether or not an AE is a result of the underlying malignancy, the AE should be submitted as a serious adverse event if it meets the appropriate seriousness criteria.

## **9.2. Assessing and Documenting Adverse Events and Hospitalizations**

Adverse event assessment will begin in conjunction with informed consent. Investigators should complete all routine and standard of care assessments to evaluate for toxicity and symptoms of drug-induced adverse events. This may include, but is not limited to, verbal reports from the patient and/or caregiver, physical examination and laboratory findings.

For all patients between informed consent and eligibility determination and for heregulin positive patients during their time on study, all adverse events, whether serious or not, will be described in the source documents and the adverse event page of the case report form. All new events, as well as those that worsen in intensity or frequency relative to baseline, which occur after first administration of study drug through the first Overall Survival follow-up visit or phone call, must be reported. However, new adverse events felt by the investigator to be related to study treatment, must be reported any time the investigator becomes aware of such an event, even if this occurrence is after the first Overall Survival follow-up. All adverse events should be followed until resolution, or until the patient discontinues from the overall survival follow-up portion of the study.

Laboratory, vital signs or ECG abnormalities are to be recorded as Adverse Events only if they are medically relevant: symptomatic, requiring corrective treatment, leading to discontinuation and/or fulfilling a seriousness criterion.

Information to be reported in the description of each adverse event includes:

- A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded)
- The date of onset of the event
- The date of resolution of the event
- A determination of whether the event is serious or not
- A determination of relatedness to the study drug
- Action taken with study drug: none; change in the study drug administration (e.g., temporary interruption in dosing); drug treatment required; non-drug treatment required; diagnostic or concomitant procedure performed; patient discontinued from the study (complete Treatment Termination case report form)
- Outcome: resolved without sequelae; resolved with sequelae; event ongoing; subject died (notify the Sponsor immediately, and complete the Serious Adverse Event page and the Subject Death page)

### **9.2.1. Hospitalizations**

Information on patient hospitalizations and/or unscheduled hospital visits should be collected in the eCRF, whether or not associated with an adverse event.

## **9.3. Reporting Serious Adverse Events**

Serious adverse events (SAE) will not be reported for patients who only sign the pre-screening consent form or for heregulin negative patients unless the serious event is directly related to a study procedure (i.e. tumor biopsy). Serious adverse event reporting will begin in conjunction

with the date of signing the main study informed consent. Any SAEs occurring prior to study drug administration that the investigator believes may have been caused by a protocol procedure must be reported immediately to the Sponsor or its designee and recorded on the case report form. Serious adverse event reporting for HRG negative patients is not required unless the event is directly related to a procedure performed for this trial.

All fatal or life-threatening adverse events must be immediately reported to the Sponsor or CRO's medical team by telephone or e-mail. Within 24 hours of the event, the Serious Adverse Event Form must be faxed to the Drug Safety Manager whether full information regarding the event is known or not. Additional follow-up by the investigator will be required if complete information is not known. De-identified source documentation of all examinations, diagnostic procedures, etc. which were completed with respect to the event should be included with the SAE form. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers (as assigned at the time of study enrollment) are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

In case of accidental or intentional overdose of study drug (seribantumab or fulvestrant), even if asymptomatic or not fulfilling a seriousness criterion, the overdose is to be reported to the Sponsor or Medical Monitor immediately (within 1 working day) using the AE and SAE forms. Overdose of study drug will be defined as  $\geq 3300$  mg of seribantumab, or  $\geq 133\%$  of planned dose of fulvestrant.

All other serious adverse events must be reported to the Drug Safety Manager within 24 hours by phone, e-mail or fax. Details are outlined in the study procedure manuals. The Serious Adverse Event Form must also be faxed to the Drug Safety Manager within 24 hours of the event whether full information regarding the event is known or not. Additional follow-up by the investigator will be required if complete information is not known.

The Medical Monitor shall be contacted as deemed necessary by the site. Current contact information shall be maintained at the site within the regulatory binder.

All serious adverse events (SAEs) will be evaluated by the Medical Monitor. If meeting the requirements for expedited reporting, the Sponsor will report the adverse event to all regulatory authorities with jurisdiction over ongoing trials with the study drug and to all other investigators involved in clinical trials with the study drug. The investigator is responsible for reporting all SAEs to the appropriate IRB/EC.

## **9.4. Determining the Severity and Relatedness of an Event**

### **9.4.1. Grading the Severity of an Adverse Event**

Each adverse event will be graded according to the NCI CTCAE V 4.03. For events not listed in the CTCAE, severity will be designated as mild, moderate, severe, or life-threatening, or fatal which correspond to Grades 1, 2, 3, 4, and 5, respectively on the NCI CTCAE, with the following definitions:

- **Mild:** an event not resulting in disability or incapacity and which resolves without intervention;
- **Moderate:** an event not resulting in disability or incapacity but which requires intervention;

- **Severe:** an event resulting in temporary disability or incapacity and which requires intervention;
- **Life-threatening:** an event in which the patient was at risk of death at the time of the event
- **Fatal:** an event that results in the death of the patient

#### 9.4.2. Relatedness to Study Drug

The investigator must attempt to determine if there exists reasonable possibility that an adverse event is related to the use of one or more study drugs, according to the following guidelines:

- **Unrelated:** This category is applicable to those AEs that are clearly due to extraneous causes (concurrent drugs, environment, etc.) and/or the clinically plausible temporal sequence is inconsistent with the onset of the event and the administration of the study drug and do not meet the criteria for drug relationship listed under UNLIKELY, POSSIBLY, PROBABLY, DEFINITELY RELATED or UNKNOWN.
- **Unlikely:** The event is clearly due to causes distinct from the use of the study drug, such as a documented pre-existing condition, the effect of a concomitant medication a new condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug
- **Possible:** The event follows a reasonable temporal sequence from administration of the study drug AND the event follows a known pathological response pattern to the study drug BUT the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug or the event could be the effect of a concomitant medication
- **Probable:** The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug AND the event cannot have been reasonably explained by an intercurrent medical condition or the event cannot be the effect of a concomitant medication
- **Definite:** The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug
- **Unknown:** Based on the evidence available, causality cannot be ascribed

#### 9.4.3. Reporting and Follow-up of Pregnancy

Patients who become pregnant while on study must immediately discontinue study treatment, and the pregnancy must be immediately reported to the Medical Monitor. Pregnancies occurring up to 6 months after the completion of the study medication must also be reported to the Sponsor.

The investigator should inform the patient of the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

In the event of a pregnancy occurring in the partner of a male patient participating in the study, the pregnant partner should be requested to report the pregnancy to the investigator, who in turn

should report it to the Sponsor. The partner should also be informed of the risks of continuing with the pregnancy, and the possible effects on the fetus.

## 10. Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and completed prior to database lock. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

### 10.1. General Considerations

Categorical variables will be summarized by frequency distributions (number and percentage of patients) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, maximum). Testing will be conducted using a one-sided 0.025/two-sided 0.05 significance level unless stated otherwise. Only 95% confidence intervals (CI) will be calculated when indicated. Descriptive statistics will be displayed in abbreviated treatment identifiers instead of seribantumab + fulvestrant, fulvestrant, and overall.

### 10.2. Statistical Hypothesis and Determination of Sample Size

The primary hypothesis is to test for differences in progression-free survival (PFS) distributions.

A stratified log-rank test will be used to analyze PFS differences with the stratification factors in the model: Statistical significance will be determined by using a one-sided type I error of 0.10. A stratified Cox proportional hazards model will be used to estimate the hazard ratio using geographic region (US, non-US) and bone-only disease (yes, no) as stratification factors.

The median PFS for the control arm (fulvestrant + placebo) is assumed to be 4.0 months in this patient population. A total of 58 PFS events will be required across two treatment arms randomized in a 1:1 ratio giving 80% power to detect a hazard ratio (HR)  $\leq 0.57$  (mPFS: 4 v 7), assuming a 1-sided significance level of 0.10. Approximately 200 patients will need to be screened in order to accrue 80 randomized in approximately 16 months with a total study duration of 20 months.

### 10.3. Analysis Populations

Patients that have signed informed consent, are identified as HRG positive based on centralized tissue analysis, and have successfully completed study entry criteria will be delineated into the following analysis populations:

- **Intent-to-Treat (ITT) population:** This population includes randomized patients. Patients will be analyzed in the randomized group.
- **Per Protocol (PP):** This population includes randomized patients. Patients will be analyzed in the randomized group. The PP population is the primary efficacy population and will only include patients that meet inclusion/exclusion criteria as defined in Section 4.1 and 4.2 and are confirmed HRG positive based on the prospective fresh centralized tissue analysis (pre-treatment tissue sample).
- **Safety (SAF) population:** The safety population includes patients receiving at least one dose of study medication. All safety analyses will be performed on this population.
- **PK population:** All treated patients with at least one PK assessment.

#### **10.4. Disposition, Demographics, and Baseline Characteristics**

Disposition of patients will be summarized, including those screened, treated, and discontinued. Reason for discontinuation will be summarized. Demographic and baseline characteristics will be summarized. Medical history and prior medications will be tabulated.

#### **10.5. Efficacy Analysis**

##### **10.5.1. Primary Efficacy Analysis**

PFS is defined as the time from randomization to the first documented radiographical progression of disease using RECIST v1.1 or death from any cause, whichever comes first. Details of censorship will be thoroughly explained in the SAP. PFS will be analyzed based on investigator assessed. The primary endpoint will be based on the investigator assessment of disease progression.

The Kaplan-Meier estimates will be used to determine median PFS and 80% CI for each treatment group. A stratified log-rank will be used to test for PFS distribution differences. A stratified Cox proportional hazards model will be used to estimate the hazard ratio and corresponding 80% confidence intervals. Stratification factors include: Geographic region (US, non-US) and bone-only disease (yes, no).

##### **10.5.2. Secondary Efficacy Analysis**

Overall Survival (OS) is defined as the time from the date of randomization to the date of death from any cause. Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date. The majority of patients are expected to live at least 2 years, therefore the proportion of deaths at the time of the PFS analysis will not be sufficient for formal hypothesis testing of OS at that time.

Various sensitivity analyses will be performed on PFS and OS which will be further detailed in the SAP. PFS and OS will also be analyzed as an unstratified log-rank test for the primary and all sensitivity analysis as well. Other analyses include a PFS sensitivity analysis performed by declaring all censors as events and testing with a stratified log-rank.

Objective Response Rate (ORR) is defined as the proportion of patients with a RECIST v1.1 response recorded from randomization until disease progression characterized as either a Complete Response (CR) or Partial Response (PR) relative to the total number of evaluable patients. Frequency and percent will be as descriptive statistics while a Cochran-Mantel-Haenszel (CMH) test stratified by stratification factor will be tested. A chi-square test without stratification will also be presented. Frequency and percent along with 95% CI will be calculated.

Time to Progression (TTP) is defined as the time from the date of randomization to the date of objective tumor progression. Those patients without objective tumor progression will be censored at the date of last tumor assessment documenting no objective progression. Patients who died prior to first scan will be censored on the date of death.

##### **10.5.3. Subgroup Analyses**

PFS will be reported for each level of stratification factor and baseline covariate to check the homogeneity of treatment effect across levels of factors as defined in the statistical analysis plan. Median values for each level of factor will be computed using Kaplan-Meier estimates. Cox

proportional hazards model will be used to calculate hazard ratios and CIs. Forest plots will be generated to display hazard ratio treatment differences across subgroups which will be defined in the SAP.

#### **10.5.4. Safety Analyses**

Safety analyses (adverse events and laboratory analyses) will be performed using the safety population. Adverse events will be coded using the latest MedDRA dictionary. Severity of adverse events will be graded according to the NCI CTCAE version 4.03.

Treatment-emergent adverse events (TEAEs) are defined as any event that occurred after the first dose of study drug and was not present prior to study drug administration or worsened in severity after study drug administration. TEAEs will be collected through the end of treatment visit. Frequency and percent summaries will be presented for treatment-emergent adverse events (TEAE) defined as adverse events that occur or worsen in severity following the first dose of seribantumab, or fulvestrant. Additional tabulations include serious adverse events (SAE), TEAE-related to seribantumab, fulvestrant and TEAE grade  $\geq 3$ , and discontinuation due to TEAE. Adverse events will be summarized by System Organ Class and preferred term. All adverse event data will be listed by patient.

Maximum and minimum decrease in continuous laboratory data will be reported. Bar graphs depicting treatment arms will be reported. Frequency and percent of abnormal laboratory values (L/ULN, 2\*L/ULN) will be assessed. Shift to most severe toxicity grade will be summarized.

Vital signs, ECG, and ECHO/MUGA will be tabulated for the change from baseline by time point. Additional analyses may be performed as described in detail within the SAP.

#### **10.5.5. Biomarker Analyses**

Biomarker data will be explored from collected tissue, as well as serum and whole blood samples, to assess potential associations with tumor response. These samples will be used to assess additional clinically relevant biomarkers. PFS, ORR, and TTP may be considered for exploratory biomarker analysis. Kaplan Meier methods for displaying graphs and Cox proportional models will be used when estimating hazard ratios with 95% confidence intervals. Biomarker analyses will be further detailed in the SAP.

#### **10.5.6. Pharmacokinetic Analyses**

Serum concentrations will be used to determine PK parameters for seribantumab and fulvestrant as appropriate using population pharmacokinetic analysis. The resulting PK parameters will be associated with efficacy and safety endpoints as appropriate. Details will be provided in a separate population PK analysis plan.

### **10.6. Data Monitoring Committee**

An independent Data Monitoring Committee (DMC) will be established to regularly monitor emerging safety data and evaluate for trial efficacy as outlined in the DMC charter. The DMC will consist of oncology and statistical experts, independent of the Sponsor. The DMC will be unblinded to randomization information. The charter of the DMC and the statistical analysis plan will be documented separately.



## **11. Study Administration**

### **11.1. Pre-Study Documentation**

Prior to initiating the trial, the investigator will provide the Sponsor or designee with the following documents:

- A signed FDA Form 1572 (or equivalent information for ex-US sites that do not permit completion of the U.S. FDA 1572 form).
- A current (i.e. updated no more than 24 months prior) curriculum vitae for the Principal Investigator and each sub-investigator listed on the FDA Form 1572 or equivalent, that is signed and dated.
- A copy of the current medical license for the investigator and each sub-investigator.
- A letter from the IRB/EC stipulating approval of the protocol, the informed consent document, and any other material provided to potential trial participants with information about the trial (e.g. advertisements)
- The current IRB/EC membership list for the reviewing IRB/EC, or the multiple project assurance number from the U.S. Federal Wide Assurance program where applicable
- A signed Investigator Protocol Agreement
- A completed financial disclosure form for the investigator and all sub-investigators
- A current laboratory certification for the local reference laboratory and curriculum vitae of the laboratory director
- A list of current laboratory normal values for the reference laboratory

### **11.2. Source Documents**

The investigator will maintain records separate from the case report forms in the form of clinic charts, medical records, original laboratory, radiology and pathology reports, pharmacy records, etc. The investigator will document in the clinic chart or medical record the date on which the patient signed informed consent prior to the patient's participation in the trial. Source documents must completely reflect the nature and extent of the patient's medical care, and must be available for source document verification against entries in the case report forms when the Sponsor's monitor visits the investigational site. Source documents regarding procedures such as scans and laboratory evaluations performed as part of the standard of care prior to enrollment in the study can be used to fulfill certain screening and baseline assessments. All information obtained from source documents will be kept in strict confidentiality. Source data sent to the Sponsor or the Sponsor's representative as supporting documentation for serious adverse events will be de-identified to preserve confidentiality.

### **11.3. Trial Ethics**

The study will be performed according to the principles of the Declaration of Helsinki, the International Conference on Harmonization Guidance on Good Clinical Practice and the requirements of the US FDA and/or local regulatory authorities regarding the conduct of human clinical trials.

### **11.4. Patient Informed Consent**

No study related procedures will be performed until a patient or a patient's legal representative has given written informed consent. The Sponsor will provide to the investigator a sample

informed consent document that includes all the requirements for informed consent according to the ICH GCP, U.S. FDA guidelines (21 CFR 31.50) and/or local regulatory guidelines. However, it is up to the investigator to provide a final informed consent that may include additional elements required by the investigator's institution. Changes to the Sponsor's sample informed consent should receive approval from the Sponsor or the Sponsor's representative prior to use in the study. The informed consent document must clearly describe the potential risks and benefits of the trial, and each prospective participant must be given adequate time to discuss the trial with the investigator or site staff and to decide whether or not to participate. Each patient who agrees to participate in the trial and who signs the informed consent form will be given a copy of the signed, dated and witnessed document. The provision of informed consent must be documented in the medical record.

### **11.5. Investigational Review Board Approval**

The trial will not be initiated until there is approval of the protocol, informed consent document and any other material used to inform the patient about the nature of the trial by the local IRB or EC. The IRB or EC should be duly constituted according to local regulatory requirements. Approval must be in the form of a letter signed by the Chairperson of the IRB/EC or the Chairperson's designee, must be on IRB/EC stationary and must include the protocol by name and/or by designated number. If an investigator is a member of the IRB/EC, the approval letter must stipulate that the Investigator did not participate in the final vote, although the investigator may participate in the discussion of the trial. The investigator will also inform the IRB/EC of any SAE that the Sponsor reports to regulatory authorities, will report on the progress of the trial at least yearly (or more frequently if required by local regulation or guidance) and will provide to the IRB/EC a final summary of the results of the trial at the conclusion of the trial.

### **11.6. Monitoring**

Overall study monitoring will be conducted through a combination of on-site visit and centralized monitoring. A risk-based, data-driven monitoring approach will be used to verify data for this trial which will also include a centralized review of data for quality, trends, consistency and general safety review. A clinical monitor will make regularly scheduled trips to the investigational site to review the progress of the trial, study data and site processes. At each visit, the monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and study manual and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

The actual frequency of monitoring trips will depend on the enrollment rate and performance at each site. The investigator will allow Merrimack Pharmaceuticals, and/or its representatives or designees, access to all pertinent medical records, as required by federal regulations, in order to allow for the verification of data gathered in the CRFs and for the review of the data collection process.

During scheduled monitoring visits, the investigator and the investigational site staff must be available to meet with the study monitor in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. In addition to on-site monitoring visits, the Sponsor and/or representatives will also be routinely reviewing data. Any queries identified

through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database.

At any time during the course of the study, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The investigator must promptly inform Merrimack Pharmaceuticals of any audit requests by health authorities, and will provide Merrimack Pharmaceuticals with the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

### **11.7. Confidentiality**

It is the responsibility of the investigator to ensure that the confidentiality of all patients participating in the trial and all of their medical information is maintained. Case report forms and other documents submitted to the Sponsor must never contain the name of a trial patient. All patients in the trial will be identified by a unique identifier which will be used on all CRF's and any other material submitted to the Sponsor. All case report forms and any identifying information must be kept in a secure location with access limited to the study staff directly participating in the trial.

#### **11.7.1. Confidentiality of Biomarker Samples**

Blood and tissue samples collected as part of the biomarker analysis will be identified only by a number assigned to the patient at the study site; this number will be used in lieu of the patient's name in order to protect the patient's identity. The samples will be stored at a facility designated by the Sponsor. Other than the patient's unique identifying number, no additional patient information will be stored with these samples. Samples will be kept until they are used completely for the specified biomarker analyses, or, in the event there is remaining tissue or blood sample available, such specimens may be stored indefinitely. At the time of informed consent, patients will be able to refuse indefinite storage of these remaining samples. If indefinite storage is refused, any remaining samples will be destroyed following the completion of the study. Similarly, patients may withdraw approval at any time by submitting a written request to the study site investigator. Upon receipt of this withdraw of consent, no further analyses will be completed and the patient's remaining samples will be destroyed; however, data already collected will not be removed from the study dataset.

Any samples that a patient consents to be stored indefinitely may be used by the Sponsor for future oncological translational work, as directed by the findings of the exploratory biomarker evaluation and the results of the initial tissue biomarker evaluation. The results from these exploratory analyses may not necessarily be shared with the investigators or the participating subjects.

### **11.8. Protocol Amendments**

The protocol will only be amended with the consent of the Sponsor and the IRB/EC. Changes to the protocol must be in the form of a written amendment; changes other than those of a simple administrative nature (e.g., a new telephone number for a medical monitor) must be submitted by the investigator to the local IRB/EC and such amendments will only be implemented after approval of the requisite IRB/EC. All amendments will also be submitted to the FDA and/or local regulatory authorities by the Sponsor.

Protocol changes to eliminate an immediate hazard to a trial patient may be implemented by the investigator immediately. The investigator must then immediately inform their IRB/EC and the Sponsor will immediately notify applicable regulatory authorities.

### **11.9. Records Retention**

The investigator will retain the records of the clinical trial (including, but not necessarily limited to, CRFs, source documents, informed consent forms, drug accountability records, IRB/EC correspondence, Sponsor correspondence, etc.) for 2 years following the date that the last marketing application for the study drug is approved (or per local regulatory requirements), or if no marketing application is filed, or if such an application is not approved, for 2 years after the formal discontinuation of clinical development of the study drug. The Sponsor or designee will notify investigators when retention of study records is no longer required. Study records must be stored in a safe and secure location permitting timely retrieval, if necessary.

Study records must be retained as per the GCP guidelines and local regulatory requirements, including, but not limited to, case report forms, signed informed consents, correspondence with the IRB/EC, study drug dispensing and inventory records, source documents (clinic charts, medical records, laboratory results, radiographic reports) and screening/enrollment logs.

Should the investigator relocate or retire the responsibility for maintaining the study records may be transferred to another investigator. The Sponsor must be notified of the identity of the individual assuming responsibility for maintaining the study records and the location of their storage. If no other individual at the site is willing to assume this responsibility, the Sponsor will assume responsibility for maintaining the study records.

### **11.10. Study Termination**

The Sponsor reserves the right to terminate the study at any site and at any time. Reasons for study termination may include, but are not limited to, the following

- Investigator non-compliance with the protocol, GCP or regulatory requirements
- Insufficient enrollment
- Safety concerns
- Drug supply or manufacturing issues
- The Sponsor's decision to modify or discontinue the development of seribantumab
- A request to discontinue the study by the FDA and/or local regulatory authorities

The Sponsor will promptly inform all investigators and the FDA and/or local regulatory authorities if the study is suspended or terminated for any reason. The investigator will promptly notify the IRB/EC if the study is suspended or terminated.



## 12. Investigator Signature Page


I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this study as outlined herein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study. I will identify study personnel conducting study specific procedures and appropriately document their training and/or delegated responsibilities. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the patients in the study.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practice (GCP).

\_\_\_\_\_  
Signature of Investigator

\_\_\_\_\_  
Date

\_\_\_\_\_  
Print Name of Investigator

  
\_\_\_\_\_  
Signature of Sponsor

5/2/17  
Date

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