CRESTONE: A Phase 2 Study of Seribantumab in Adult Patients with Neuregulin-1 (NRG1) Fusion Positive Locally Advanced or Metastatic Solid Tumors

Elevation Oncology, Inc.

Protocol Number:	ELVCAP-001-01
Investigational Product:	Seribantumab
IND Number:	100605
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Replaces Protocol Version	6.0 (15 August 2022)

Sponsor:
Elevation Oncology, Inc.
888 Seventh Avenue
12th Floor
New York, NY 10106

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AKT	Protein kinase B
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
C_{avg}	Average serum concentration
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Clearance
C_{max}	Maximum serum concentration
C_{min}	Minimum serum concentration
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
ErbB	Epidermal growth factor family of receptor tyrosine kinases
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
ERK	Extracellular signal-regulated kinases
FDA	Food and Drug Administration
FISH	Fluorescence in-situ hybridization
GCP	Good Clinical Practice
HER2	Human epidermal growth factor receptor 2
HER3	Human epidermal growth factor receptor 3
ICH	International conference on harmonization
Ig	Immunoglobulin
IMA	invasive mucinous lung adenocarcinoma
INTS9	Integrator Complex Subunit 9
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
IV	Intravenous(ly)
MAPK	Mitogen-activated protein kinase

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MM-121	Seribantumab
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NCI	National Cancer Institute
NGS	Next generation sequencing
NRG	Neuregulin
NSCLC	Non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall survival
PCM1	Pericentriolar Material 1
PCR	Polymerase chain reaction
PDAC	Pancreatic ductal adenocarcinoma
PDX	Patient derived xenograft
PFS	Progression-free survival
PI3K	Phosphatidylinositol-3-kinase
PK	Pharmacokinetic(s)
PMEPA1	Prostate Transmembrane Protein, Androgen Induced 1
PR	Partial response
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QLQ-C30	Quality of Life Questionnaire-Core 30
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SRC	Safety Review Committee
TEAE	Treatment-emergent adverse events
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
US	United States

STUDY SYNOPSIS

Sponsor:	Elevation Oncology, Inc. 888 Seventh Avenue, 12th Floor New York, NY 10106
Protocol Title:	A Phase 2 Study of Seribantumab in Adult Patients with Neuregulin-1 (NRG1) Fusion Positive Locally Advanced or Metastatic Solid Tumors
Protocol Number:	ELVCAP-001-01 (CRESTONE)
Phase of Development:	Phase 2
Study Locations:	International
Number of sites:	Approximately 40-50 sites worldwide.
Patient Population:	Patients with locally advanced or metastatic solid tumors that harbor NRG1 gene fusion as assessed by local molecular assays, such as PCR, NGS (RNA or DNA) or Fluorescence in situ hybridization (FISH) testing. Patients must have progressed on or after at least one prior standard therapy appropriate for their tumor type and stage of disease, with no further available curative therapy options. Patients who discontinued prior therapy due to intolerance or unacceptable toxicity may be eligible after discussion with the Sponsor.
Estimated Number of Patients:	An estimated 90 patients will be enrolled.
Primary Objective:	To determine the objective response rate (ORR) by independent radiologic review to single agent seribantumab (anti-HER3 targeted therapy; 3,000 mg weekly) in patients with centrally confirmed NRG1 gene fusion positive advanced cancer according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Secondary Objectives:	• To determine the overall efficacy of single agent seribantumab in NRG1 fusion positive patients with various solid tumors through the assessment of the following clinical outcome parameters:
	  • Duration of Response (DoR) by independent radiologic review
	  • ORR and DoR by investigator assessment
	  • Progression-free Survival (PFS) by independent radiologic review and investigator assessment
	  • Overall Survival (OS)
	  • Clinical Benefit Rate (CR, PR, SD ≥ 24 weeks) by independent radiologic review and investigator assessment
	• To describe the safety profile of seribantumab.

Exploratory Objectives:	• To evaluate the pharmacokinetics of the seribantumab dosing schedule in patients with NRG1 gene fusion positive advanced solid tumors. • To evaluate if mechanistically linked exploratory biomarkers from tumor tissue or blood samples correlate with clinical outcomes. • To evaluate changes from baseline in quality of life, as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30).
Study Design:	This study is an open-label, international, multi-center, Phase 2 study in adult patients with locally advanced or metastatic solid tumors, which harbor the NRG1 gene fusion based upon local testing. The design of the study is summarized in Figure 1. All patients will be determined to be NRG1 gene fusion positive based on local testing of tumor tissue per local laboratory directed analyses prior to initiating further screening procedures. After all screening procedures and determination of eligibility for study treatment (including local NRG1 fusion positive testing result) have been completed, eligible patients will be assigned by the Sponsor to the appropriate cohort based upon prior treatment history. Patients will be assigned to Treatment Cohorts as follows: **Cohort 1:** Patients with NRG1 gene fusions who are ERBB/HER2/HER3 treatment-naïve AND harbor NRG1 gene fusions with an EGF-like domain intact. Cohort 1 will include at least 55 patients who have received ≥ 1 prior standard first-line therapy in the locally advanced or metastatic setting. **Cohort 2:** Enrollment to Cohort 2 was closed under Protocol Version 5.0/Protocol Administrative Letter 8.0. Patients with NRG1 gene fusions with an EGF-like domain intact, who received ≥ 1 prior standard first-line therapy in the locally advanced or metastatic setting including at least one ERBB/HER2/HER3 directed treatment are ineligible for study participation. **Cohort 3:** Enrollment to Cohort 3 was closed under Protocol Version 5.0 and later. Patients with NRG1 fusions without an EGF-like domain (including but not limited to NRG1-PMEPA1, NRG1-STMN2, PCM1-NRG1 and INTS9-NRG1) and patients with NRG1 fusions and other molecular aberrations lacking standard treatment options, AND patients unable to provide tissue for central confirmation of NRG1 gene fusion status are ineligible for study participation under Protocol Version 5.0. One cycle of treatment consists of 28 days. Dosing begins at the Cycle 1 Week 1 (C1W1) visit. Treatment consists of seribantumab 3,000 mg 1-h IV once weekly until patients meet one or more protocol-specific treatment discontinuation criteria. Dose modifications (Section 5.3) and/or treatment interruptions

	(Section 5.2.4.3) to manage treatment related toxicities are permitted during weekly dosing. After 12 months of weekly dosing, patients who have tumor response (CR or PR) per RECIST v1.1 may transition from treatment with seribantumab 3,000 mg once every week to once every 2 weeks (Q2W) after discussion with and approval from the Sponsor. Note: Previous dosing regimens for patients enrolled under prior protocol versions are described in detail in Appendix A. Patients are expected to be treated until investigator-assessed progressive disease or unacceptable toxicity. Treatment beyond progression is permitted if the Investigator determines that the patient may derive clinical benefit from continued exposure to seribantumab. Tumor assessments will be measured and recorded by the local radiologist beginning at weeks 6, 12, 18 and 24 with a ± 2-week window and subsequently every 8 weeks (± 2 weeks) through Week 48, followed by every 12 weeks (± 2 weeks) beginning at Week 60 until disease progression and evaluated using the RECIST guidelines (version 1.1). Patients that discontinue study treatment for reasons other than disease progression including due to toxicities will continue to receive tumor assessments as outlined above until initiation of next anti-cancer therapy, clinical disease progression, death, or withdrawal of consent. In addition, an independent central review of scans will be conducted. All images will be submitted to a central imaging facility for this purpose and will be assessed by independent reviewers in accordance with the Imaging Charter. After patients discontinue seribantumab treatment, survival information and information about subsequent therapies will be collected until death or study closure, whichever occurs first. An optional biopsy may be obtained at the time of progression to explore mechanisms of seribantumab resistance.
Inclusion Criteria:	To be eligible for participation in the study, patients must meet the following inclusion criteria: • Locally advanced or metastatic solid tumor with an NRG1 gene fusion identified through molecular assays, such as PCR, NGS (RNA or DNA) or FISH, by a CLIA-certified or similarly accredited laboratory. • Availability of fresh or archived formalin-fixed, paraffin-embedded tumor sample to be submitted to a central laboratory for post-enrollment confirmation of NRG1 gene fusion status. • Patients must have progressed on or after at least one prior standard therapy appropriate for their tumor type and stage of disease, with no further available curative therapy options. Patients who discontinued prior therapy due to intolerance or unacceptable toxicity may be eligible after discussion with the Sponsor. • Age ≥ 18 years. • Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2.

	• Patients must have at least one measurable extra-cranial lesion as defined by RECIST v1.1 (Eisenhauer et al., 2009).
	• Adequate organ function defined as:
	  • Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) < 2.5 × upper limit of normal (ULN), or AST and ALT < 5 × ULN if liver function abnormalities due to underlying malignancy.
	  • Total bilirubin < 2.0 × ULN. Patients with a known history of Gilbert's Disease and an isolated elevation of indirect bilirubin are eligible. Patients with documented hepatic involvement are eligible if total bilirubin is ≤ 3.0 × ULN.
	  • Estimated glomerular filtration rate ≥ 30 mL/minute using the Cockcroft-Gault formula:
	  $\frac{(140 - \text{age}) \times \text{body weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} \times 0.85$ (if female)
	  • Absolute neutrophil count ≥ 1.0×10^9/L not requiring growth factor support for at least 7 days prior to C1W1, and
	  • Platelet count ≥ 75×10^9/L not requiring transfusion support for at least 7 days prior to C1W1.
	  • Hemoglobin ≥ 8.0 g/dL not requiring transfusion support for at least 7 days prior to C1W1.
	• Able to provide informed consent or have a legal representative able and willing to do so.
	• Ability to comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation.
	• Willingness of men and women of reproductive potential to observe conventional and effective birth control for the duration of treatment and for 3 months following study completion. Please refer to Section 4.1 for detailed criteria for men and women of reproductive potential.

Exclusion Criteria:	To be eligible for participation in the study, patients must not meet any of the following exclusion criteria: • Additional alterations in known oncogenes other than NRG1 fusion that could confer resistance to seribantumab monotherapy treatment, including alterations for which there are approved targeted therapies. Genomic testing reports from locally obtained molecular testing documenting NRG1 fusion must be submitted to the Sponsor for review during the screening period. • Life expectancy < 3 months • Pregnant or lactating • Prior treatment with pan-ERBB or any ERBB/HER2/HER3 directed therapy (exclusion for Cohort 1 only). • Symptomatic or untreated brain metastases

	○ ***Note:*** *Patients with asymptomatic brain metastases treated with radiation or surgery and without evidence of progression by imaging at screening are eligible to participate in the study, including those on a stable [i.e., same dose for ≥ 2 weeks] low-dose corticosteroid regimen. Refer to Section 5.5.* ○ ***Note****: Patients with history of brain metastases or if clinically indicated will require brain imaging at baseline and subsequent serial scans if brain metastases are present at baseline.* • Received other systemic anticancer therapy (investigational or standard chemotherapy, immunotherapy, or targeted therapy) within 28 days prior to planned start of seribantumab or 5 half-lives, whichever is shorter. • Prior to initiation of seribantumab treatment, patients must have recovered from clinically significant toxicities from prior anticancer or investigational therapy or acute radiation toxicities. • Any other active malignancy requiring systemic therapy. • Known hypersensitivity to any of the components of seribantumab or previous CTCAE grade 3 or higher hypersensitivity reactions to fully human monoclonal antibodies. • Clinically significant cardiac disease, including symptomatic congestive heart failure, unstable angina, acute myocardial infarction within 6 months of planned first dose, or unstable cardiac arrhythmia requiring therapy (including torsades de pointes), or prolongation of the QT interval corrected for heart rate (QTcF) > 470 ms on at least 2 of 3 consecutive electrocardiograms (ECGs), and mean QTcF > 470 ms on all three ECGs during screening. Correction of suspected drug-induced QTcF prolongation may be attempted at the investigator's discretion if considered clinically safe. • Active uncontrolled systemic bacterial, viral, or fungal infection. • Patients who are not appropriate candidates for participation in this clinical study for any other reason as deemed by the investigator.
Length of Study:	It is intended that patients will be treated until radiographic disease progression per RECIST v1.1, death or intolerable toxicity, as assessed by the investigator. It is estimated that enrollment to Cohort 1 (a minimum of 55 patients with centrally confirmed NRG1 gene fusion positive cancer) will require 36 months.
Investigational Product:	Seribantumab is a fully human IgG2 monoclonal antibody that binds to human epidermal growth factor receptor 3 (ERBB3/HER3). Seribantumab is a clear liquid solution, supplied in sterile, single-use vials for injectable use at a concentration of 25 mg/mL. Seribantumab drug product should be stored at 2-8°C.
Sample Size:	At least 55 patients with centrally confirmed NRG1 gene fusion positive cancer will be enrolled in the Cohort 1 primary efficacy analysis population. This sample size will provide approximately 90% power for

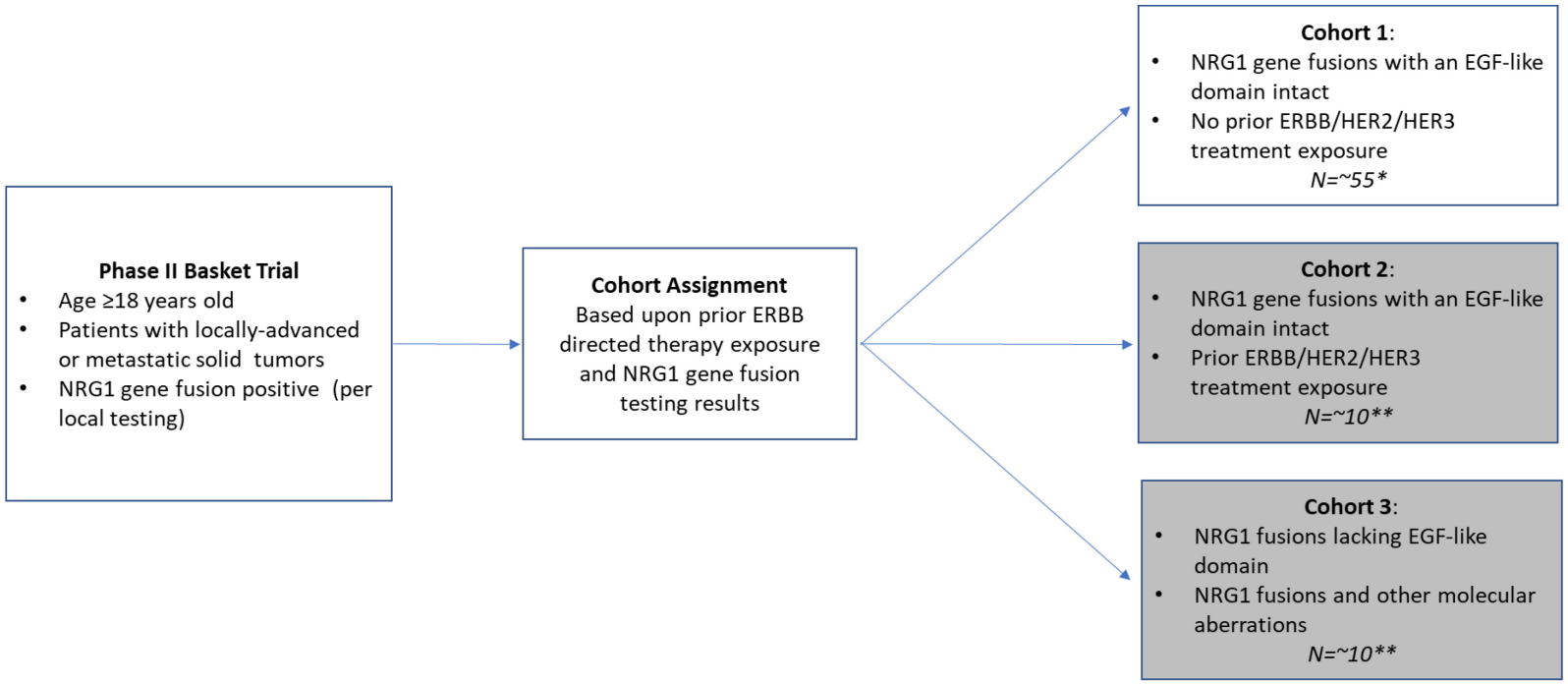
	the lower bound of the 95% CI to exclude 20% assuming the ORR is 40% with seribantumab treatment. With the release of Protocol Version 5.0, Cohort 3 was closed to enrollment. Under Protocol Version 5.0/Protocol Administrative Letter 8.0, Cohort 2 was closed to enrollment.
Statistical Considerations and Data Reporting:	**General:** In general, all analyses will follow the multi-cohort nature of the study design. Categorical variables will be summarized by frequency distributions (number and percentages of patients) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, maximum). **Analysis Populations:** The analysis populations to be used for the planned statistical analyses include: **Efficacy Analysis Populations** • **Cohort 1 primary efficacy analysis population** Analyses of the Cohort 1 primary efficacy analysis population will be intended to support a potential registration. It will include Cohort 1 patients enrolled in this study who meet all criteria listed below: • Centrally confirmed NRG1 gene fusion. • Received at least one dose of seribantumab at 3,000 mg QW dosing regimen (starting with Protocol Version 3.0 and later). Patients in the safety-run in (enrolled under Protocol Version 2.0 or earlier) will be included if they received seribantumab at 3,000 mg QW beyond induction/re-induction. • Received at least one prior standard therapy in the locally advanced or metastatic setting. • At least one measurable lesion at baseline as assessed per RECIST v1.1 based on independent central review. • **Cohort 2 and Cohort 3 efficacy analysis population** These populations will be used for exploratory efficacy analysis by investigator-assessments for each cohort, respectively. All patients enrolled in each cohort who received at least one dose of seribantumab and had at least one measurable lesion at baseline assessed per RECIST 1.1 based on investigator assessments will be included in the analysis. With the release of Protocol Version 5.0, Cohort 3 was closed to enrollment. Under Protocol Version 5.0/Protocol Administrative Letter 8.0, Cohort 2 was closed to enrollment. **Safety analysis population:** The safety analysis population includes patients receiving at least one dose of seribantumab therapy across any of the three treatment cohorts (e.g., Cohort 1, 2, and 3) and across any of the

	seribantumab dosing regimens. The safety population will be used for the overall safety analysis. **Primary Efficacy Analysis:** ORR is determined by RECIST v1.1 (confirmed CR+PR) and will be assessed by independent radiographic review. To be assigned a status of confirmed PR or CR, changes in tumor measurements must be confirmed by repeated assessments at least 4 weeks (28 days) after the criteria for response are first met. The point estimate of the ORR along with the 2-sided 95% CI exact Clopper-Pearson CI will be presented. For the Cohort 1 primary efficacy analysis population, the lower bound of the 95% CI will be compared with the 20% threshold. **Secondary Efficacy Analysis:** ORR based on the investigator assessments will be analyzed similarly as described for the primary efficacy analysis. This is considered a sensitivity analysis. DoR is defined as the time from the start date of CR or PR (whichever response status is observed first and subsequently confirmed), to the date of first documented radiographical progression of disease using RECIST v1.1, or death from any cause, whichever comes first. DoR will be calculated for patients who are responders, i.e., those who achieve a confirmed CR or PR. The initiation of new anticancer therapy will mean the end of the response for the calculation of DoR. PFS is defined as the time from the date of seribantumab treatment initiation (Dose 1) to the first documented radiographical progression of disease using RECIST 1.1, or death from any cause, whichever comes first. The Kaplan-Meier method will be used to estimate PFS for each treatment cohort. OS is defined as the time from the date of seribantumab treatment initiation (Dose 1) to the date of death from any cause. The Kaplan-Meier method will be used to estimate OS for each treatment cohort. In addition to estimating the overall distribution for OS, the median and the 12-month survival rate will be estimated. Additional sensitivity analyses may be conducted for the efficacy endpoints and the details are specified in the statistical analysis plan. **Safety Analysis:** The safety analysis will be based on the Safety Analysis Population and will be presented by cohort and all cohorts combined. Patient incidence of all treatment-emergent adverse events (TEAE) will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Summary tables of TEAEs that are fatal, serious, treatment-related, Grade 3 or 4, TEAEs leading to dose reduction or

	interruption of study drug, and TEAEs leading to permanent discontinuation of study drug will be provided. Changes in lab values and vital signs over time will be summarized. Summary of treatment exposure will be provided to include treatment duration, number of doses, actual total dose administered, and relative dose intensity. **Safety Review Committee:** A Safety Review Committee (SRC) has been established to monitor study conduct and to assess the safety and tolerability and PK (if available) of seribantumab. The SRC initially convened after the first 6 patients completed treatment with Induction Regimen 1 and once again after the next 6 patients completed treatment with Induction Regimen 2. Beginning with the first patient enrolled to the 12-week Target Induction Regimen under Clinical Protocol Version 3.0, and subsequently for patients enrolled to the weekly dosing regimen under Protocol Versions 4.0 and later, the SRC meetings will occur on a monthly basis for 6 consecutive months to ensure the safety and tolerability of the 3,000 mg 1-h IV once weekly dosing regimen. Overall 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 will be graded according to the NCI CTCAE Version 5.0. Treatment-emergent adverse events (TEAEs), TEAE grade 3 and higher, TEAE-related, serious adverse events (SAEs), and discontinuation due to AE will be reported by frequency and percent summaries. Adverse events will be summarized by System Organ Class and preferred term. All adverse event data will be listed by patient. Laboratory, vital signs, and ECG data will be summarized according to parameter type. An expanded SRC will be convened to conduct an interim analysis after 20 patients have been enrolled and treated in Cohort 1 and followed for at least one post-baseline tumor assessment (i.e., 6 weeks ± 2 weeks). The expanded SRC will consist of the SRC members described in Section 3.3, which details the addition of two independent members consisting of one clinician and one biostatistician. Following the interim analysis, the Sponsor will revert to the original SRC to continue monitoring of the safety and conduct of the study. **Exploratory Analyses:** Biomarker Analysis: Biomarker data from collected tissue and whole blood will be used to evaluate if biomarkers from tumor tissue or blood samples correlate with clinical outcomes. Efficacy outcomes considered in these exploratory analyses will include ORR, OS, and PFS. Kaplan Meier methods will be used in these descriptive analyses. PK and Anti-seribantumab Immunogenicity Analysis: Plasma concentrations by patient, cycle, day, and time will be obtained and documented prior to and following seribantumab dosing at timepoints specified in Section 6.2. Serum samples to assess immunogenicity and the

	presence of anti-seribantumab immunogenicity will be collected at timepoints specified in Section 6.2. Quality of Life Analysis: The QLQ-C30 will be administered at visits associated with disease assessments as specified in Section 6.2 to assess changes from baseline in quality of life.

Figure 1: Study Schema of Patient Flow in the CRESTONE Clinical Study



*Cohort 1 will include at least 55 patients that have received ≥1 prior standard first-line therapy in the metastatic setting. **More than 10 patients may enroll under Cohorts 2 and 3 with Sponsor approval. Shaded box indicates cohort is closed to enrollment

EGF = epidermal growth factor; ERBB = receptor tyrosine-protein kinase erbB-3; HER = human epidermal growth factor receptor; NRG1 = Neuregulin-1

1. INTRODUCTION

1.1. NRG1 Overview

Neuregulin-1 or NRG1 (formerly known as heregulin or HRG) is a cell adhesion molecule that is encoded by the NRG1 gene found on the short arm of chromosome 8 (8p12) in humans. The gene encodes a membrane glycoprotein that mediates cell-cell signaling and plays a critical role in the growth and development of multiple organ systems (Online Mendelian Inheritance in Man database entry accessed 29 August 2019).

There are four neuregulin genes [NRG1-4], and approximately 30 different neuregulin isoforms, which are generated through alternative splicing of their mRNA. These different isoforms probably have different roles in different tissues. Type I NRG1, contains an N-terminal immunoglobulin (Ig)-like domain prior to the EGF-like domain, which is followed by a specific hydrophobic stretch and a unique C-terminal domain (Trombetta et al., 2017).

Neuregulin 1 (NRG1) is the predominant binding ligand for the v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (ErbB3 or HER3), an oncogene that is overexpressed in a variety of cancers and is associated with tumor pathogenesis and resistance to therapy. ErbB3/HER3 is one member of a family of 4 human growth factor receptors: HER3, HER4, ErbB1 (EGFR) and ErbB2 (HER2). All family members consist of a glycosylated extracellular domain, a single hydrophobic transmembrane segment, and an intracellular portion with a juxtamembrane segment, a protein kinase domain, and a carboxyterminal tail (Roskoski 2014). Upon binding their cognate ligand, the receptors homo- or heterodimerize, which activates downstream signaling pathways. HER2 does not have a ligand, but rather partners preferentially with HER3 when other ERBB family members are ligand-activated (Dimou et al., 2019).

Thus, under normal circumstances wild-type NRG1 binds to the extracellular domain of HER3 and induces its heterodimerization with HER2, its preferential dimerization partner. Following auto-and trans-phosphorylation of intracellular tyrosine residues, downstream effector kinases of the Mitogen-activated protein kinase/ extracellular signal-regulated kinases (MAPK/ERK) and Phosphoinositide 3-kinases, Protein kinase B (PI3K-AKT) pathways then become active. Any dysregulation of this tightly controlled process can lead to pathologic signaling via MAPK and other canonical pathways, leading to unregulated cellular proliferation.

1.2. NRG1 Fusions

Rearrangement of the neuregulin-1 gene (*NRG1*) leading to a *DOC4-NRG1* fusion was first identified in a breast cancer cell line in 1997 (Schaefer et al., 1997). The molecular change was then shown to be present in breast cancer samples (Huang et al., 2004), in invasive mucinous adenocarcinomas (IMA) of the lung [CD74–NRG1, (Fernandez-Cuesta et al., 2014)] and other tumor types (Jonna et al., 2019). Over the past 5 years, general knowledge related to the biology, incidence and prevalence of NRG1 genomic alterations has increased considerably. The most comprehensive study of the incidence of *NRG1* fusions across multiple tumor types is derived from molecular testing of 21,858 tumor specimens collected from September 2015-December 2018 (Jonna et al., 2019). As depicted in Figure 2, comprehensive RNA-based next generation sequencing (NGS) testing identified the presence of *NRG1* fusions across a broad array of solid

tumors including non-small cell lung carcinoma (NSCLC), gallbladder cancer, renal cell carcinoma, bladder cancer, ovarian cancer, pancreatic cancer, breast cancer, neuroendocrine tumor, sarcoma, and colorectal cancer. While this comprehensive study suggests the overall incidence of *NRG1* fusions is approximately 0.2%, the prevalence of NRG1 fusions appears to be enriched in certain solid tumor settings, including patients with IMA (7-27%; Shim HS et al., 2015 and Shin DH et al., 2016) as well as those diagnosed with KRAS wild-type pancreatic ductal adenocarcinoma (6%; Jones et al., 2019).

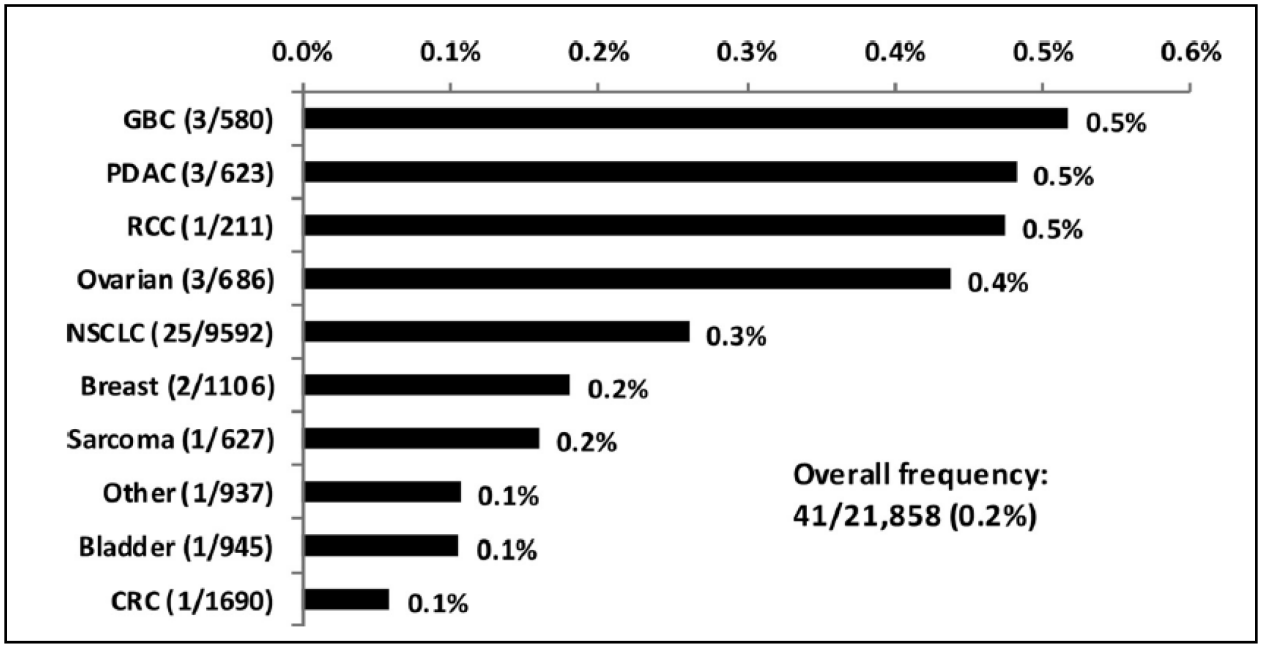


Figure 2: Incidence of NRG1 gene fusions by tumor type

In addition to its role as an oncogenic driver, *NRG1* fusions have also been identified as a mediator of resistance to alectinib in anaplastic lymphoma kinase (*ALK*)-rearranged NSCLC (McCoach et al., 2018). The largest category of *NRG1* fusions identified mostly involve the upstream gene *CD74* and contain the active *EGF*-like domain encoded by exon 6. Although at least 4 fusions have also been reported without an active EGF-like domain, NRG1-PMEPA1, NRG1-STMN2, PCM1-NRG1 (Drilon et al., 2018) and INTS9 (Ke et al., 2019), these are unlikely to be oncogenic, as the EGF domain has been shown to be essential for oncogenic transformation (Shin et al., 2016).

NRG1 fusions as primary drivers are mutually exclusive with most other known oncogenic drivers such as *EGFR*, *KRAS, ALK*, *ROS1* and *RET* in nearly all tumor samples tested. This is supported by case reports of *NRG1* fusions in pancreatic adenocarcinoma and lung cancer with wild-type KRAS phenotype. Heining et al., 2018 reported four wild-type KRAS patients of which 3 out of 4 harbored an *NRG1* fusion, whereas a recent article described 3/47 or 6% of pancreatic adenocarcinoma patients with wild-type *KRAS* who also tested for *NRG1* fusions (Jones et al., 2019).

1.3. Rationale for Targeting the HER3 Pathway in NRG1 Fusion Dependent Cancer

NRG1 is a ligand for HER3, and generation of NRG1 fusion proteins disrupts normal cellular signaling pathways. NRG1 fusion pathogenesis has been shown to occur through the indiscriminate heterodimerization of HER3/ERBB3 with a defective NRG1 gene, which leads to constitutive activation of the ERBB2/ERBB3 signaling pathway and downstream activation of growth and survival pathways, which drive tumor formation and progression (Fernandez-Cuesta 2014).

Preventing NRG1 from binding HER3 and initiating a signaling cascade that drives tumorigenesis, represents a promising concept of targeting NRG1-induced oncogenesis. Anti-HER3 monoclonal antibodies inhibit NRG1 fusion proteins, containing active EGF-like domains, from binding to HER3, thus halting the formation of active HER2/HER3 complexes and preventing downstream signaling and uncontrolled growth and proliferation of cancer cells. In contrast, anti-HER2 antibodies are only able to prevent heterodimerization of HER3 with HER2, thereby still allowing NRG1 binding to HER3 and heterodimerize with other HER family member (e.g., HER1/EGFR or HER4). Inhibition of HER2 pathway signaling alone does not adequately suppress growth and signaling pathways in NRG1 fusion positive patients. More recently, tyrosine kinase inhibitors (TKIs) targeting HER2 and other ERBB family members, such as the pan-ERBB inhibitor afatinib, have been evaluated in NRG1 fusion positive patients. In one multicenter, global registry experience, afatinib produced a 33% response rate (3 partial responses [PRs], 1 complete response [CR]) in 12 patients with metastatic lung cancer, however 50% of patients progressed within 2 months of treatment initiation and two of the four responders experienced short-lived responses of 2.0 and 4.4 months, respectively (Duruisseaux et al., 2019). In addition to this report from the NRG1 Global Registry, Table 1 highlights several published case reports related to the use of afatinib in NRG1 positive patients with various advanced solid tumors. Similar to the findings in the global registry, afatinib was associated with short-lived partial responses of < 3 months in the majority of these published case reports.

In contrast to the experience with afatinib, one case report exists where a patient who had progressed following exposure to four lines of prior chemotherapy and immunotherapy, developed a prolonged PR (19 months) following treatment with an anti-HER3 directed antibody (GSK2849330). Coupled with the encouraging preclinical findings for anti-HER3 approaches, this case report suggests a potentially important role for HER3 directed therapy over HER2 or pan-ERBB directed therapy in NRG1 fusion positive patients (Drilon et al., 2018).

Targeting tumors harboring NRG1 fusions by using either a HER3 mAb and/or a combination of anti-HER3 and HER2 treatments, represent the most encouraging therapeutic strategies for rare NRG1 fusion driven cancers. A summary of published case reports, including experience with the pan-ERBB inhibitor afatinib, is summarized in Table 1.

Table 1: Clinical Case Reports for ERBB/HER Directed Treatment of NRG1 Fusion Positive Cancers

Drug(s)	Tumor Type	HER/ERBB targeted drug	NRG mutation	Response	Response Duration (months)	Reference
Afatinib	NSCLC	Pan-HER TKI	*SDC4-NRG1*fusion	PR	12	Jones 2017
Afatinib	Cholangio-carcinoma	Pan-HER TKI	*ATP1B1-NRG1*fusion	PR	8	Jones 2017
Afatinib	NSCLC	Pan-HER TKI	*SLC3A2-NRG1* fusion	PR	12	Gay 2017
Afatinib	NSCLC	Pan-HER TKI	*CD74-NRG1* fusion	PR	10	Gay 2017
Afatinib	IMA	Pan-HER TKI	*CD74–NRG1* fusion	PR	6	Cheema 2017
Afatinib	Pancreatic	Pan-HER TKI	*ATP1B1–NRG1* fusion	PR	3	Heining 2018
Afatinib	Colorectal	Pan-HER TKI	*NRG1-POMK* fusion	SD	9+	Weinberg 2019
Afatinib	Liver cancer	Pan-HER TKI	*APP-NRG1* fusion	PR	7+	Weinberg 2019
Afatinib	Prostate/ colon	Pan-HER TKI	*ATP1B1-NRG1* fusion	PR	5.5	Weinberg 2019
Erlotinib/ pertuzumab	Pancreatic	EGFR TKI + anti-HER2 mAb	*SARAF-NRG1* fusion	PR	3	Heining 2018
Erlotinib/ Lumretuzumab	IMA	EGFR TKI + anti-HER3 mAb	*NRG1-SLC3A2* fusions	SD	4	Kim 2018
Erlotinib/ Lumretuzumab	IMA	EGFR TKI + anti-HER3 mAb	*NRG1-SLC3A2* fusions	SD	4	Kim 2018
GSK2849330	IMA	Anti-HER3 mAb	*CD74-NRG1* fusion	PR	19	Drilon 2018
MCLA-128	PDAC	HER2/HER3 bispecific mAb	*ATP1B1-NRG1* fusion	PR	7+	Schram 2019
MCLA-128	PDAC	HER2/HER3 bispecific mAb	*ATP1B1-NRG1* fusion	SD	7+	Schram 2019
MCLA-128	NSCLC	HER2/HER3 bispecific mAb	*CD74-NRG1*fusion	PR	4.5+	Schram 2019

CR = complete response; EGFR = Epidermal growth factor receptor; HER = human epidermal growth factor receptor; IMA = invasive mucinous adenocarcinoma; NRG = neuregulin; NSCLC = non-small cell lung carcinoma; PDAC = pancreatic ductal adenocarcinoma; PR = partial response; SD = stable disease; TKI = tyrosine kinase inhibitor

1.4. Seribantumab

Seribantumab (formerly MM-121) is a fully human, monoclonal IgG2 antibody that binds to the NRG1 domain of the ErbB3 receptor with single digit nanomolar affinity. By preventing NRG1 from binding to the ErbB3 receptor, seribantumab effectively blocks heterodimer formation of the ErbB3 (HER3) receptor with ErbB2 (HER2) and EGFR (HER1) and as such potently blocks downstream signaling activation and cancer cell survival.

In addition to the extensive nonclinical characterization and testing, seribantumab has been intravenously (IV) administered as described in Section 1.6. Prior to its redirected development for NRG1 fusion driven cancers, seribantumab had been primarily studied in advanced cancer patients (e.g., NSCLC, breast, ovarian) with NRG1 amplified cancer. All future development of seribantumab will focus on *NRG1* gene fusion positive cancers.

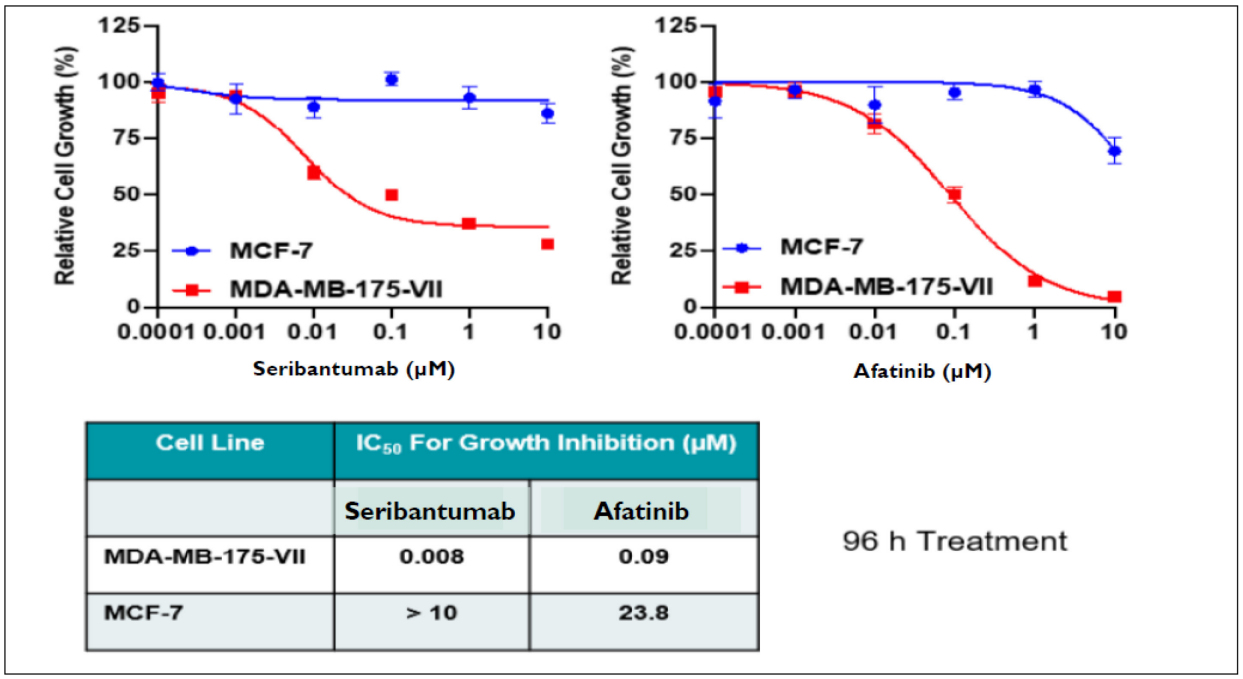
1.5. Seribantumab Nonclinical Experience in NRG1 Fusion Models

Extensive prior nonclinical testing has demonstrated that seribantumab is a sub-nanomolar inhibitor of ligand-dependent ERBB3/HER3 signaling, inhibits HER3 dimerization with HER2 and other HER family members (EGFR/HER1), and downregulates the expression of ERBB3 across many different cancers alone and in combination (Schoeberl et al., 2017). In NRG1 fusion driven cancers, ERBB3 inhibition may be more optimal than ERBB2 or pan-ERBB inhibition (Drilon et al., 2018). The effects of seribantumab in NRG1 fusion positive *in vitro* and *in vivo* models have been explored to support the redirected development of seribantumab in the NRG1 gene fusion population and this ongoing phase 2 study. Please refer to the current version of the Investigator's Brochure for a more comprehensive description of the nonclinical results demonstrating the potential of seribantumab for the treatment of patients with tumors harboring *NRG1* gene fusions.

The effects of seribantumab were recently evaluated in NRG1 fusion dependent cell lines (Odintsov et al., 2021a). As depicted in Figure 3, seribantumab was associated with potent growth inhibition (IC_{50}: 0.008 µM – shown; IC_{90}: 2.86 µM – not shown) in the MDA-MB-175-VII breast cancer cell line (DOC4/NRG1 fusion dependent cell line known to be sensitive to HER3 and HER2 inhibition), yet was not associated with growth inhibition in the MCF-7 breast cancer cell line which does not harbor the NRG1 fusion. In this same MDA-MB-175-VII cell line, seribantumab effectively inhibited HER2-HER3 dimerization and downregulated the expression of HER3 (Figure 4). Furthermore, seribantumab demonstrated complete inhibition of HER2, HER3 and HER4 downstream signaling (e.g., AKT/ERK) in this NRG1-dependent model (Figure 5), indicating the potential for HER3 directed therapy to have profound effects on ERBB pathway activity.

In an experiment evaluating the effects of seribantumab in a NRG1 lung cancer xenograft model, a single flat dose of seribantumab (0.6 mg, 0.75 mg or 1 mg per mouse) was administered and tumors were removed at 2-, 24-, or 168-hours post-drug administration, to determine impact on HER2 and HER3 phosphorylation and downstream signaling activity. As shown in (Figure 6), all doses of seribantumab resulted in reduced phosphorylation of HER2, HER3, AKT, and ERK1/2 by the 2h time point, with higher doses being more effective at the longer time points. However, at the 24h and 168h time points, reactivation of HER3, AKT and ERK1/2 protein phosphorylation was observed, despite consistent inhibition of HER2. These results suggest the frequency of initial

seribantumab administration to patients harboring oncogenic NRG1 fusions may require weekly dosing, in order achieve maximal, durable inhibition of HER3/NRG1 oncogenesis. (Odintsov et al., 2021a).



Cell Line	IC_{50} For Growth Inhibition (μM)	
	Seribantumab	Afatinib
MDA-MB-175-VII	0.008	0.09
MCF-7	> 10	23.8

96 h Treatment

Figure 3: *In Vitro* Effects of Seribantumab on NRG1 Gene Fusion Positive Breast Cancer Cell Lines

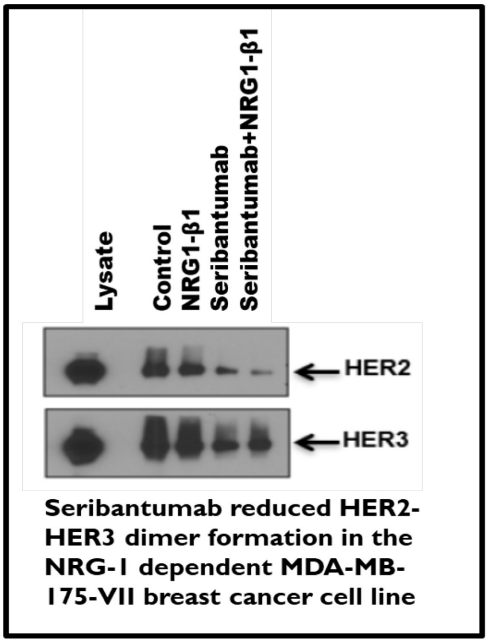


Figure 4: Seribantumab HER2/HER3 Dimer Inhibition

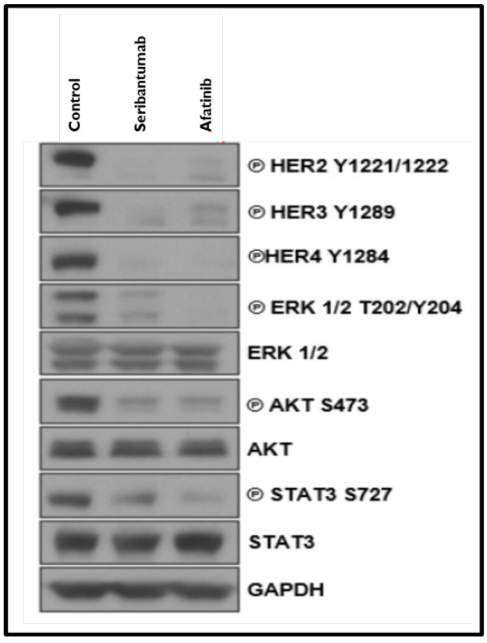


Figure 5: Seribantumab HER2, HER3, HER4 + AKT/ERK Inhibition

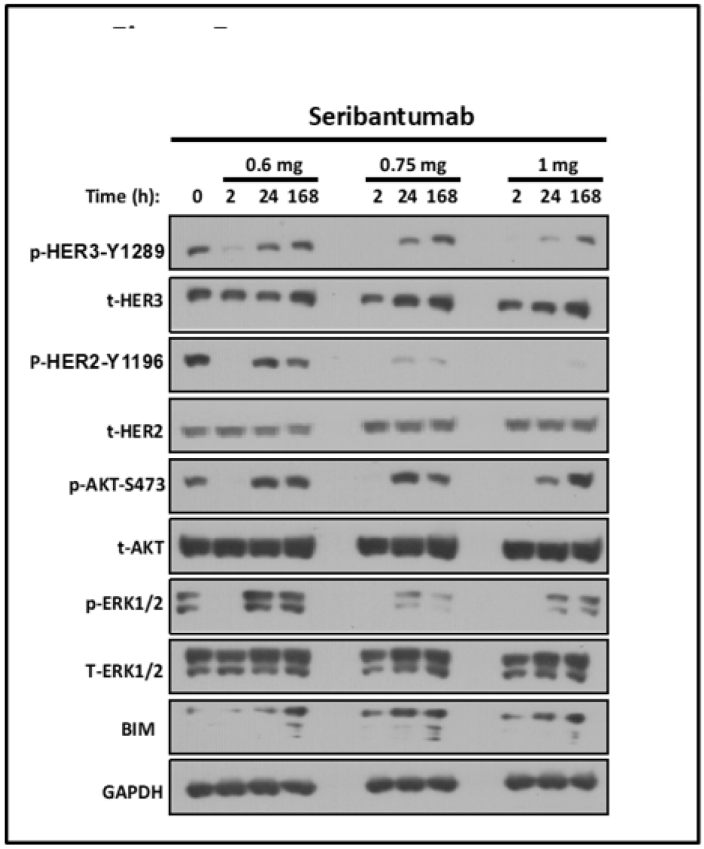


Figure 6: Efficacy of single-dose seribantumab in a NSCLC (SLC3A2-NRG1 fusion) PDX model.

The LUAD-0061AS3 patient derived xenograft (PDX) model was developed from a lung cancer specimen with a SLC3A2-NRG1 fusion and this model was used to test repeat dosing of seribantumab *in vivo* (Odintsov et al., 2021b). Notably, this specimen was derived from a patient who had progressed after prior standard therapy and progression on afatinib therapy. In this study, PDX tumors (approximately 3 mm^3) were implanted subcutaneously into the flanks of immunodeficient mice. Treatment was initiated when the tumors reached a volume of 100-150 mm^3. Each treatment group consisted of seven mice while five mice were used in the vehicle control group. Treatment started on day 14 of the experiment and consisted of vehicle (phosphate buffered saline), seribantumab (0.6, 0.75, or 1 mg per dose bi-weekly, which based upon allometric scaling for a 70 kg patient represents a human dose range of 156 – 260 mg), or afatinib (5, 10, or 15 mg/kg once daily). Figure 7 shows a dose-related decline in tumor volume across all doses of seribantumab, with the best response observed with the 1 mg dose where maximal tumor regression was approximately 60%. Notably, the pan-ErbB family inhibitor afatinib was not associated with tumor regression at the clinically equivalent dose of 5 mg/kg, however tumor regression of approximately 30% was observed at a dose of 15 mg/kg, which is approximately 3-fold higher than the clinically equivalent dose of 40 mg/day in humans. (Odintsov et al., 2021a).

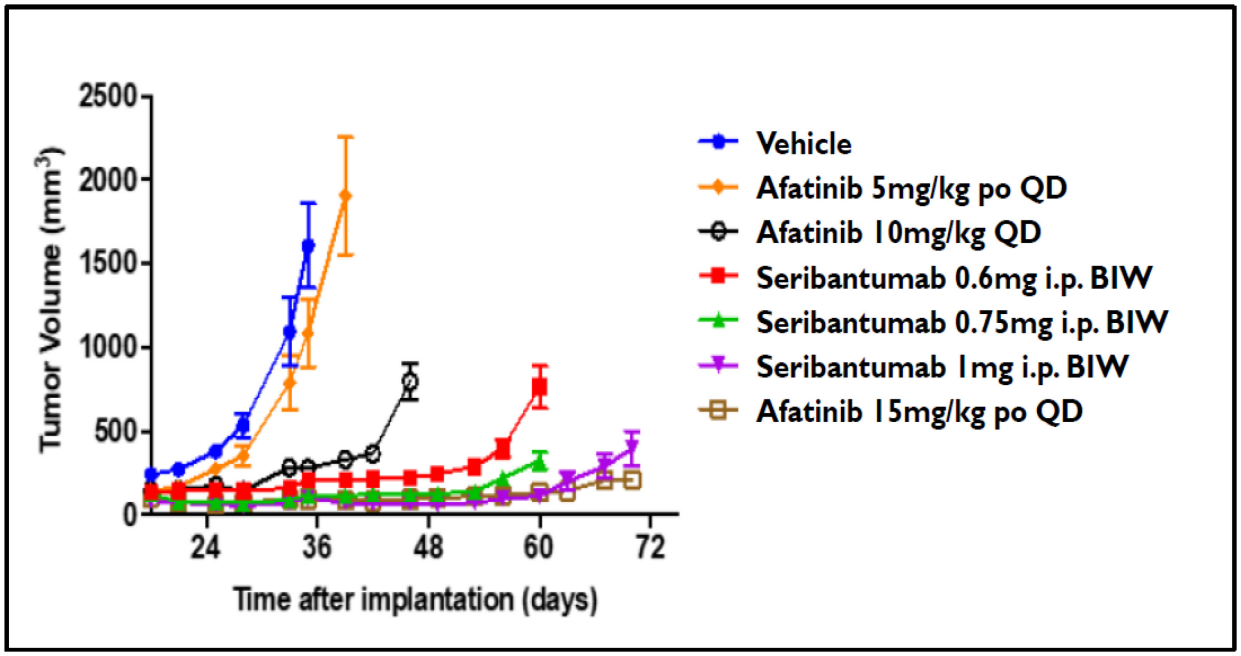


Figure 7: Seribantumab Effectively Inhibits Growth of LUAD-0061AS3 PDX NRG1 Dependent Tumors

In a separate experiment, the antitumor effects of higher doses of seribantumab (1 mg, 2.5 mg, 5 mg, or 10 mg BIW), which based upon allometric scaling for a 70 kg patient represents a human dose range of 260 – 2,600 mg, were assessed in a CLU-NRG1 ovarian cancer xenograft model. As shown in Figure 8, near complete and complete tumor regressions were observed across the entire dose range, with complete tumor regressions observed in nearly all animals at the highest dose level of 10 mg BIW, which is similar to a human dose of 2,600 mg or 2.6 grams (Odintsov et al., 2021a). In a related study, using this same ovarian CLU-NRG1 xenograft model, a single-dose pharmacokinetics (PK) study was performed at doses of 1 mg, 5 mg and 10 mg. Results from this single-dose PK study indicate the seribantumab trough (C_{min}) concentrations ranged from 200 mg/L to 880 mg/L, with an average trough concentration of 508.4 mg/L at the 10 mg dose level. With biological activity observed across the entire dose range and noting the 10 mg dose is similar to the recommended 3,000 mg human dose, these results suggest the target trough concentration should be in the range of 500 mg/L to achieve optimal target inhibition.

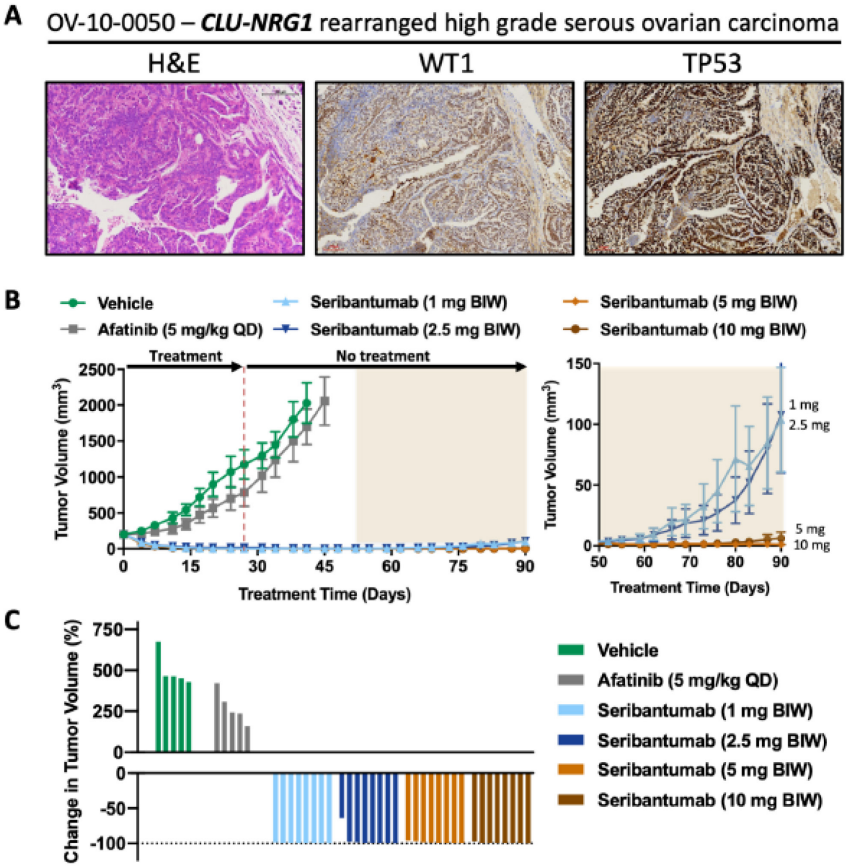


Figure 8: Efficacy of seribantumab in CLU-NRG1 ovarian cancer PDX model.

BIW = biweekly; H&E = Hematoxylin and eosin; IHC = immunohistochemistry; QD = once daily; WT = wild-type

(A) Immunohistochemical characterization of the OV-10-0050 PDX model. Hematoxylin and eosin staining, WT1 and TP53 IHC (left to right).

(B) Mice bearing OV-10-0050 PDX tumors (5-8 animals per group) were treated with vehicle, or afatinib (5mg/kg QD) or the doses of seribantumab shown (BIW). Treatment was terminated on day 27 and animals were monitored for tumor regrowth until tumors reached maximum allowable size or until 90 days after treatment initiation. Results represent the mean tumor volume ± SE. The right panel shows a zoom-in view on tumor volumes during the last 40 days of monitoring of seribantumab-treated groups. The highest dose of seribantumab blocked tumor regrowth after cessation of treatment.

(C) Change in volume of individual tumors (day 27 vs volume at start of treatment).

In a separate experiment, the anti-tumor activity of seribantumab was assessed in the APP-NRG1 pancreatic cancer PDX model. In this model, where the doubling time of the tumor in vehicle control was 7.3 days, the anti-tumor activity of seribantumab at 5 mg and 10 mg BIW was significantly greater than afatinib at a dose of 5 mg/kg. As shown in Figure 9, the tumor growth inhibition (TGI) for seribantumab was similar at both dose levels (102% and 105% at day 20, respectively), when repeat doses were administered over several weeks. These results demonstrate that frequent, repeat doses of seribantumab may achieve and maintain inhibition of HER3 pathway signaling and downstream activity. These results suggest that weekly seribantumab dosing may be necessary to achieve optimal HER3 / NRG1 inhibition. (Odinstov et al., 2021b).

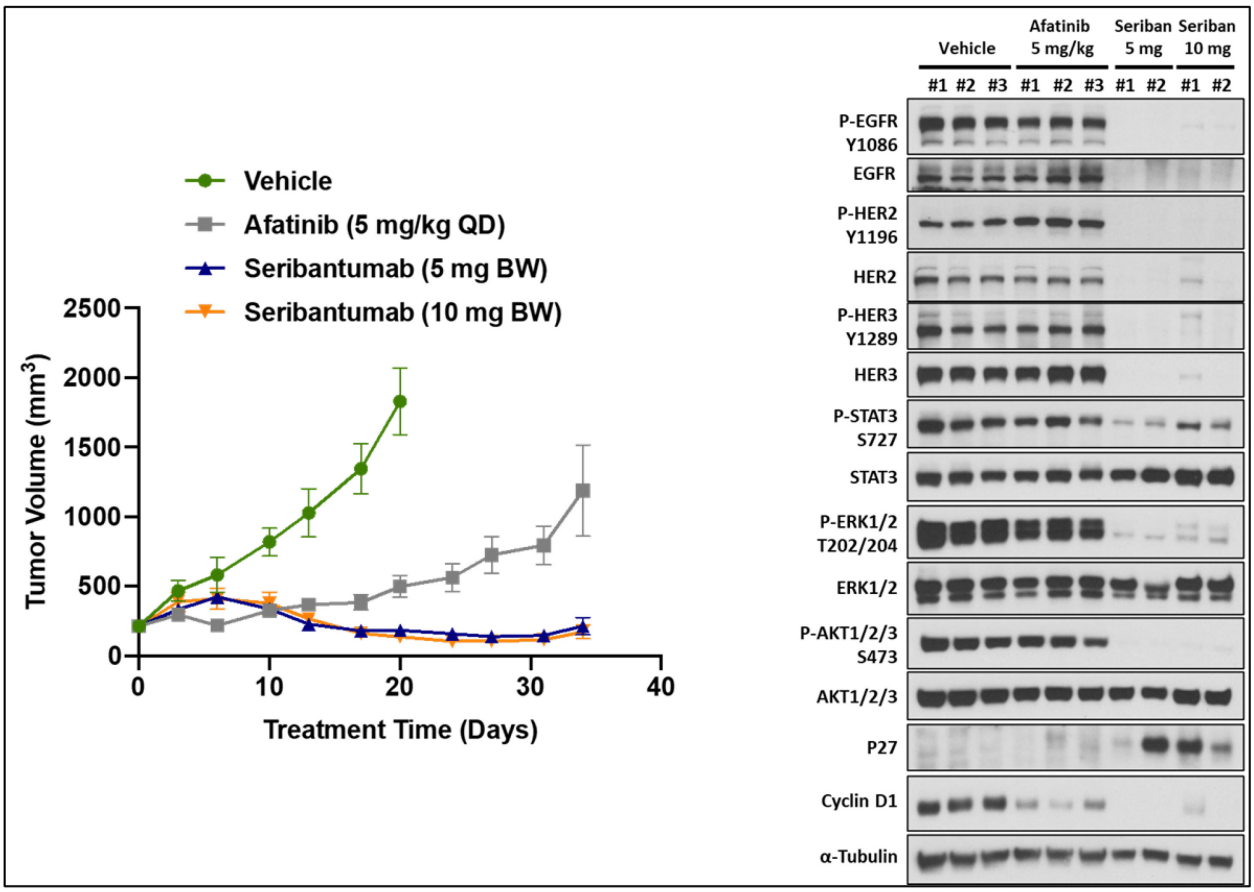


Figure 9: Efficacy of seribantumab in APP-NRG1 pancreatic cancer PDX model.

Combined, these nonclinical results demonstrate that seribantumab is effective at both *in vitro* and *in vivo* inhibition of NRG1-dependent tumorigenesis in breast, lung, ovarian and pancreatic cancer models (Odintsov et al., 2021a; Odintsov et al., 2021b). These results support the ongoing clinical evaluation of seribantumab in NRG1 fusion positive advanced solid tumors with the optimized dosing regimen consisting of seribantumab 3,000 mg 1-h IV once weekly, as outlined in Section 5.2.3.1.

1.6. Clinical Experience with Seribantumab to Date

Overall, as of May 2021, seribantumab has been administered to 869 patients in ongoing and completed studies across Merrimack's 12 studies including monotherapy treatment (n = 43), in a single patient IND as monotherapy (n = 1), and in combination with other anticancer treatment (n = 803), as well as Elevation Oncology's CRESTONE study (n = 15) and Investigator Sponsored INDs (n = 7) in patients with tumors harboring NRG1 gene fusions. The PK and safety findings indicate that seribantumab is well tolerated as monotherapy and in combination therapy with targeted therapies, antiestrogen, and other standard chemotherapy (see current version of Investigator's Brochure).

1.6.1. Prior Clinical Development of Seribantumab

Previously, seribantumab was being developed by Merrimack Pharmaceuticals to investigate the effects of seribantumab as combination therapy with standard anticancer therapies. The focus of these studies were tumors where NRG1 was overexpressed or amplified, and not tumors harboring NRG1 gene fusions. Please refer to the current version of the Investigator's Brochure for additional information regarding the previous development of seribantumab under Merrimack or the single patient IND study, as well as a safety summary of identified risks to date for seribantumab in combination with other anticancer therapies.

1.6.2. Clinical Development of Seribantumab in NRG1 Fusion Positive Cancer

The current Sponsor, Elevation Oncology, redirected the clinical development activities for seribantumab to focus exclusively on the treatment of NRG1 gene fusion driven cancers with seribantumab monotherapy. In September 2020, Elevation Oncology treated the first patient in the phase 2 CRESTONE study to evaluate the effects of seribantumab monotherapy in patients with NRG1 fusion positive advanced solid tumors that have received ≥1 prior standard first-line therapy in the metastatic setting.

The final safety run-in cohort of six (6) patients has completed full induction treatment with Induction Regimen 2 and no DLT was reported. After formal review, the Safety Review Committee (SRC) recommended treatment with Induction Regimen 2, for all subsequently enrolled patients.

Safety findings are discussed in Section 5.2.5. Refer to the current version of the Investigator's Brochure for additional details.

1.6.3. Rationale for 3,000 mg Once Weekly Dosing

The dosing regimen (3,000 mg, once weekly) for the CRESTONE study was selected based on the non-clinical findings in NRG1 fusion models (Section 1.5), safety considerations from prior clinical studies of seribantumab, two PK simulation studies, and clinical PK data observations in NRG1 fusion patients treated with seribantumab (refer to the current version of the Investigator's Brochure for additional details). The following has been demonstrated:

- In non-clinical mouse data, HER3 pathway activity rebounds within 24 to 168 hours following a single dose of seribantumab (Figure 6).
- Multiple repeat doses of seribantumab on a weekly basis are required to produce sustained tumor growth inhibition and ongoing HER3 pathway inhibition (Figure 9).
- Seribantumab has demonstrated activity across a range of doses and tumor models, with results indicating higher doses are associated with maximal tumor regression and inhibition of HER3 / NRG1 oncogenesis.
- In a single-dose PK study in the ovarian cancer PDX model, the seribantumab trough concentration ranged from 200 mg/L (1 mg/mouse dose) to 880 mg/L (10 mg/mouse dose), with an average trough concentration equal to 508.4 mg/L at the 10 mg dose level. The 10 mg dose level in this model is similar to a 2,600 mg human dose, based upon allometric scaling for a 70 kg patient, suggesting that optimal target inhibition

may require trough concentrations ≥ 500 mg/L in patients harboring oncogenic NRG1 gene fusions.

- Clinical PK data (steady-state trough concentrations of seribantumab) obtained in 16 patients confirmed the accuracy of the PK simulation predictions (Table 2 [Data on file, Feb 2021; PK Simulation Report]) – trough seribantumab levels associated with the dose of 3,000 mg weekly at steady-state were approximately 550 mg/L, which achieved the preclinical efficacy exposure target; lower or less frequent dosing yielded lower trough.
- Based upon the preliminary PK findings, there were no correlations observed between exposure (C_{max} or C_{min}) and frequency or grade of TEAEs.

Based upon these non-clinical and clinical observations, the dosing regimen for the CRESTONE study is being modified as outlined in Section 5.2.3.1. The revised treatment regimen will consist of seribantumab 3,000 mg 1-h IV weekly until progressive disease, toxicity or other treatment discontinuation criteria are met. The switch to the weekly dosing regimen is supported by the clinical observations to date, where weekly dosing for the initial 4 weeks (induction regimen dosing) has been safe and very well tolerated at the fixed 3,000 mg 1-h IV weekly dose. A summary of simulation results for select dosing scenarios is presented in Table 2 (Data on file, Feb 2021; PK Simulation Report):

Table 2: Summary of PK Simulations for Initial CRESTONE Regimen and Extended Weekly Regimens

Dosing Regimen[a]	Dosing Period[a]	$C_{trough,avg}$ (95% CI) (mg/L)	$C_{ss,avg}$ (95% CI) (mg/L)	$C_{max,avg}$ (95% CI) (mg/L)
Initial CRESTONE regimen (Protocol v2.0)	Weeks 4-18 (Q2W) Weeks 18-28 (Q3W)	285 (72-612) 199 (31-468)	682 (362-1141) 539 (264-893)	1128 (319-2445) 912 (190-2270)
12-week Induction (3,000 mg QW x 12 weeks); 3,000 mg Q2W maintenance	Weeks 4-12 (QW) Weeks 12-28 (Q2W)	592 (223-1122) 314 (75-720)	1321 (703-2186) 753 (437-1133)	2207 (1133-3571) 1255 (362-2626)
16-week Induction (3,000 mg QW x 16 weeks); 3,000 mg Q2W maintenance	Weeks 4-16 (QW) Weeks 16-28 (Q2W)	594 (208-1172) 329 (75-747)	1324 (705-2171) 771 (358-1323)	2213 (1132-3705) 1275 (358-2644)

[a] Each dosing regimen includes the same initial treatment consisting of 3,000 mg IV weekly (QW) x 4 doses (Weeks 0 to 3)

1.7. Risk/Benefit Assessment for 3,000 mg Once Weekly Dosing

Based upon the safety, tolerability and clinical experience with Induction Regimen 1 (n=6) and Induction Regimen 2 (n=6) through April 2021, the seribantumab dosing regimen has been modified for all subsequently enrolled patients to 3,000 mg 1-h IV once weekly.

This optimized seribantumab regimen, consisting of 3,000 mg once weekly dosing, is expected to be safe and well tolerated, while offering NRG1 fusion patients the opportunity to rapidly achieve and maintain optimal seribantumab exposure and maximal inhibition of HER3 / NRG1 oncogenesis. With this weekly dosing regimen, patients will be observed more frequently during

their weekly clinic visits and safety monitoring and oversight will occur more frequently by the SRC, as outlined in Section 3.2.

2. OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to determine the objective response rate (ORR) by independent radiologic review to single agent seribantumab (anti-HER3 targeted therapy; 3,000 mg weekly) in patients with centrally confirmed NRG1 gene fusion positive advanced cancer according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

2.2. Secondary Objectives

The secondary objectives of this study include the following:

- To determine the overall efficacy of single agent seribantumab in NRG1 gene fusion positive patients with various solid tumors through the assessment of the following clinical outcome parameters:
  - Duration of Response (DoR) by independent radiologic review
  - ORR and DoR by investigator assessment
  - Progression-free Survival (PFS) by independent radiologic review and investigator assessments
  - Overall Survival (OS)
  - Clinical Benefit Rate (CR, PR, SD ≥ 24 weeks) by independent radiologic review and investigator assessment
- To describe the safety profile of seribantumab

2.3. Exploratory Objectives

The exploratory objectives for this study are:

- To evaluate the pharmacokinetics of the seribantumab dosing schedule in patients with NRG1 gene fusion positive advanced solid tumors
- To evaluate if mechanistically linked exploratory biomarkers from tumor tissue or blood samples correlate with clinical outcomes
- To evaluate changes from baseline in quality of life, as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30)

3. STUDY DESIGN

3.1. Overview of Study Design

This study is an open-label, international, multi-center, phase 2 study in adult patients with advanced or metastatic solid tumors, which harbor the NRG1 gene fusion based upon local testing.

All patients will be determined to be NRG1 gene fusion positive based on local testing of tumor tissue per local laboratory directed analyses prior to initiating further screening procedures. After all screening procedures and determination of eligibility for study treatment (including local NRG1 fusion positive testing result) have been completed, eligible patients will be assigned by the Sponsor to the appropriate cohort based upon prior treatment history. Patients will be assigned to Treatment Cohorts as follows:

Cohort 1: Patients with NRG1 gene fusions who are ERBB/ HER2/HER3 treatment-naïve AND harbor NRG1 gene fusions with an EGF-like domain intact. Cohort 1 will include at least 55 patients who have received ≥1 prior standard first-line therapy in the locally advanced or metastatic setting.

Cohort 2: Enrollment to Cohort 2 was closed under Protocol Version 5.0/Protocol Administrative Letter 8.0 Patients with NRG1 gene fusions with an EGF-like domain intact, who have received ≥1 prior standard first-line therapy in the locally advanced or metastatic setting including at least one ERBB/HER2/HER3 directed treatment are ineligible for study participation.

Cohort 3: Enrollment to Cohort 3 was closed under Protocol Version 5.0 and later. Patients with NRG1 fusions without an EGF-like domain (including but not limited to NRG1-PMEPA1, NRG1-STMN2, PCM1-NRG1, and INTS9-NRG1) and patients with NRG1 fusions and other molecular aberrations lacking standard treatment options AND patients unable to provide tissue for central confirmation of NRG1 gene fusion status are ineligible for study participation under Protocol Version 5.0.

One cycle of treatment consists of 28 days. Dosing begins at the Cycle 1 Week 1 (C1W1) visit. Treatment with seribantumab will be as described in Section 5.2.3.1. Dose modifications (Section 5.3) and/or treatment interruptions (Section 5.2.4.3) to manage treatment related toxicities are permitted during weekly dosing. After 12 months of weekly dosing, patients who have tumor response (CR or PR) per RECIST v1.1 may transition from treatment with seribantumab 3,000 mg once every week to once every 2 weeks (Q2W) after discussion with and approval from the Sponsor. Previous dosing regimens for patients enrolled under prior protocol versions are described in detail in Appendix A.

Patients are expected to be treated until Investigator-assessed progressive disease or unacceptable toxicity. Treatment beyond progression is permitted if the Investigator determines that the patient may derive clinical benefit from continued exposure to seribantumab. Tumor assessments will be measured and recorded by the local radiologist beginning at weeks 6, 12, 18, and 24 with a ± 2-week window and subsequently every 8 weeks (± 2 weeks) through Week 48, followed by every 12 weeks (± 2 weeks) beginning at Week 60 until disease progression. Tumor assessments will be evaluated using the RECIST v1.1 guidelines. Patients that discontinue study treatment for reasons other than disease progression including due to toxicities will continue to receive tumor assessments as outlined above until initiation of next anti-cancer therapy, clinical disease

progression, death, or withdrawal of consent. In addition, an independent central review of scans will be conducted. All images will be submitted to a central imaging facility for this purpose and will be assessed by independent reviewers in accordance with the Imaging Charter. After patients discontinue seribantumab treatment, survival information and information about subsequent therapies will be collected until death or study closure, whichever occurs first. An optional biopsy may be obtained at the time of progression to explore mechanisms of seribantumab resistance.

3.2. Safety Review Committee

A SRC has been established to monitor study conduct and to assess the safety and tolerability and PK (if available) of seribantumab. The SRC initially convened after the first 6 patients completed dosing with Induction Regimen 1 and once again after the next 6 patients completed treatment with Induction Regimen 2. Beginning with the first patient enrolled to the 12-week Target Induction Regimen under Clinical Protocol Version 3.0 and subsequently for patients enrolled to the once weekly dosing regimen under Clinical Protocol Versions 4.0 and later, the SRC meetings will occur on a monthly basis for 6 consecutive months to ensure the safety and tolerability of the 3,000 mg 1-h IV once weekly dosing regimen. Safety analyses are described in Section 10.6. Further details will be provided in the SRC Charter.

3.3. Expanded Safety Review Committee for Interim Futility Analysis

An expanded SRC will be convened to review data from a pre-planned interim analysis. The interim analysis based on ORR will be conducted after 20 patients have been enrolled and treated in Cohort 1 and followed for at least one post-baseline tumor assessment (i.e., 6 weeks ± 2 weeks). The expanded SRC will be composed of the current members of the SRC with the addition of one independent clinician and one independent biostatistician for the interim analysis only. Following the interim analysis, the Sponsor will revert to the original SRC to continue monitoring of the safety and conduct of the study.

Enrollment may continue while the expanded SRC is evaluating the data from the first 20 patients in Cohort 1. Should four or more objective responses be observed at the time of the pre-planned interim analysis, enrollment to Cohort 1 will continue until a minimum of 55 patients with centrally confirmed NRG1 gene fusion have been consented, screened, and treated with seribantumab. The interim analysis is described in Section 10.7.

4. STUDY POPULATION

The target population for this study will be NRG1 gene fusion positive patients with locally advanced or metastatic solid tumors. Patients must have progressed on or after at least one prior standard therapy appropriate for their tumor type and stage of disease, with no further available curative therapy options. Patients who discontinued prior therapy due to intolerance or unacceptable toxicity may be eligible after discussion with the Sponsor. 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.

a. Locally advanced or metastatic solid tumor with an NRG1 gene fusion identified through molecular assays, such as PCR, NGS (RNA or DNA) or fluorescence in situ hybridization (FISH), by a Clinical Laboratory Improvement Amendments (CLIA)-certified or similarly accredited laboratory.
b. Availability of fresh or archived formalin-fixed, paraffin-embedded tumor sample to be submitted to a central laboratory for post-enrollment confirmation of NRG1 gene fusion status (see also Section 4.3).
c. Patients must have progressed on or after at least one prior standard therapy appropriate for their tumor type and stage of disease, with no further available curative therapy options. Patients who discontinued prior therapy due to intolerance or unacceptable toxicity may be eligible after discussion with the Sponsor.
d. Age ≥ 18 years.
e. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2
f. Patients must have at least one measurable extra-cranial lesion as defined by RECIST v1.1
g. Adequate organ function defined as:

- Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) < 2.5 × upper limit of normal (ULN), or AST and ALT < 5 × ULN if liver function abnormalities due to underlying malignancy
- Total bilirubin < 2.0 × ULN. Patients with a known history of Gilberts Disease and an isolated elevation of indirect bilirubin are eligible. Patients with documented hepatic involvement are eligible if total bilirubin ≤ 3.0 × ULN.
- Estimated glomerular filtration rate ≥ 30 mL/minute using the Cockcroft-Gault formula:

  $$\frac{\textbf{(140 – age) x body weight (kg)}}{\textbf{Serum creatinine (mg/dL) × 72}} \times \textbf{0.85 (if female)}$$

- Absolute neutrophil count ≥ 1.0 × 10^9/L at Screening and not requiring growth factor support for at least 7 days prior to C1W1, and
- Platelet count ≥ 75 × 10^9/L at Screening not requiring transfusion support for at least 7 days prior to C1W1
- Hemoglobin ≥ 8.0 g/dL at Screening and not requiring transfusion support for at least 7 days prior to C1W1

h. Able to provide informed consent or have a legal representative able and willing to do so
i. Ability to comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation
j. Willingness of men and women of reproductive potential to observe conventional and effective birth control for the duration of treatment and for 3 months following study completion.

Notes:

- A postmenopausal woman will be defined as having no menses for 12 months without an alternative medical cause. Male sterility will be defined as only men sterilized surgically. For male patients with a pregnant partner, a condom should be used for contraception. For male patients with a non-pregnant female partner of child-bearing potential and woman of child-bearing potential one of the following birth control methods with a failure rate of less than 1% per year when used consistently and correctly are recommended:

  - Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation given orally, intravaginally, or transdermally
  - Progestogen-only hormonal contraception associated with inhibition of ovulation given orally, by injection, or by implant
  - Intrauterine device
  - Intrauterine hormone-releasing system
  - Bilateral tubal occlusion/ligation
  - Vasectomized partner
  - Sexual abstinence
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

- Birth control methods unacceptable for this clinical study are:
  - Periodic abstinence (calendar, symptothermal, or post-ovulation methods)
  - Withdrawal (coitus interruptus)
  - Spermicide only
  - Lactational amenorrhea method

4.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in this study:

k. Additional alterations in known oncogenes other than NRG1 fusion that could confer resistance to seribantumab monotherapy treatment, including alterations for which there are approved targeted therapies. Genomic testing reports from locally obtained molecular testing documenting NRG1 fusion must be submitted to the Sponsor for review during the screening period
l. Life expectancy < 3 months
m. Pregnant or lactating
n. Prior treatment with pan-ERBB or any ERBB/HER2/HER3 directed therapy (exclusion for Cohort 1 only)
o. Symptomatic or untreated brain metastases

– ***Note:*** *Patients with asymptomatic brain metastases treated with radiation or surgery and without evidence of progression by imaging at screening are eligible to participate in the study, including those on a stable [i.e., same dose for ≥ 2 weeks] low-dose corticosteroid regimen. Refer to Section 5.5.*

– ***Note****: Patients with history of brain metastases or if clinically indicated will require brain imaging at baseline and subsequent serial scans if brain metastases are present at baseline.*

p. Received other systemic anticancer therapy (investigational or standard chemotherapy, immunotherapy, or targeted therapy) within 28 days prior to planned start of seribantumab or 5 half-lives, whichever is shorter
q. Prior to initiation of seribantumab treatment, patients must have recovered from clinically significant toxicities from prior anticancer or investigational therapy or acute radiation toxicities
r. Any other active malignancy requiring systemic therapy
s. Known hypersensitivity to any of the components of seribantumab or previous National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher hypersensitivity reactions to fully human monoclonal antibodies
t. Clinically significant cardiac disease, including symptomatic congestive heart failure, unstable angina, acute myocardial infarction within 6 months of planned first dose, or unstable cardiac arrhythmia requiring therapy (including torsades de pointes), or prolongation of the QT interval corrected for heart rate (QTcF) > 470 ms on at least 2 of 3 consecutive ECGs, and mean QTcF > 470 ms on all three ECGs during screening. Correction of suspected drug-induced QTcF prolongation may be attempted at the investigator's discretion if considered clinically safe
u. Active uncontrolled systemic bacterial, viral, or fungal infection
v. Patients who are not appropriate candidates for participation in this clinical study for any other reason as deemed by the investigator

4.3. Archival or Fresh Tumor Specimen Requirements

This study will only enroll patients with NRG1 gene fusion positive tumors. A patient's tumor NRG1 fusion status will be identified by a molecular assay such as PCR, NGS (RNA or DNA) or FISH as routinely performed by a CLIA-certified or other similarly accredited laboratory. For patients who do not have adequate archived tumor tissue available for testing, a fresh tumor biopsy will be obtained in advance of study participation, if it can be safely performed per Section 8.6.1. The local NRG1 fusion testing methodologies may vary for qualified sites.

In addition, an adequate archival or fresh tumor sample will also be required for NRG1 gene fusion confirmation using a qualified RNA-based NGS test performed by a central laboratory following enrollment and assignment to Cohort 1. Tissue obtained from exploratory Cohort 2 will support development of companion diagnostic and future exploratory biomarker research. Refer to the Laboratory Manual for additional details on tumor tissue collection.

5. STUDY TREATMENT

5.1. Treatment Assignment

If a patient is determined to be NRG1 gene fusion positive based upon local testing, investigators will determine if the patient meets all other eligibility criteria. A copy of the redacted molecular pathology report identifying the NRG1 gene fusion per local testing used for eligibility and a list of the patient's prior anti-cancer treatments with dates must be submitted for Sponsor review prior to patient enrollment. Once all study enrollment criteria have been fulfilled, patients will be assigned to the appropriate treatment cohort based upon prior ERBB treatment history. Following enrollment, investigators and/or site staff will submit the required tumor samples to a central laboratory for confirmation of NRG1 fusion status per the laboratory manual.

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 injection 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 or retest date 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 Dosing, Preparation and Administration

5.2.3.1. Seribantumab Dosing

Patients enrolled will initiate treatment with seribantumab 3,000 mg 1-h IV once weekly until patients meet one or more protocol-specific treatment discontinuation criteria.

In the setting of weekly dosing, it is expected that during the course of treatment patients may need to miss doses for non-adverse event related reasons; for example, due to weather conditions making travel to the clinic difficult, due to holidays or vacation, etc. After the patient has been on treatment for at least 6 cycles, occasional missed doses during weekly dosing for non-adverse event related reasons would not constitute protocol deviations. No more than one missed dose in

an 8 week period is permissible. A discussion should be held with the Sponsor if the patient falls below 80% compliance with the assigned dosing regimen.

Dose modifications (Section 5.3) and/or treatment interruptions (Section 5.2.4.3) to manage treatment related toxicities are permitted during weekly dosing.

After 12 months of weekly dosing, patients who have tumor response (CR or PR) per RECIST v1.1 may transition from treatment with seribantumab 3,000 mg once every week to once every 2 weeks (Q2W) after discussion with and approval from the Sponsor.

For previous seribantumab dosing schedules, see Appendix A.

5.2.3.2. Preparation and Administration

Administration of seribantumab will require multiple vials, all of which should originate from the same lot number. Seribantumab should be brought to room temperature prior to mixing with 0.9% normal saline. Vials should not be shaken. The appropriate quantity of study drug will be removed from the vial and further diluted with 0.9% normal saline to a final total volume of 250 mL and administered over 60 minutes (±15 minutes) using a low protein binding 0.20 or 0.22 micron in-line filter. All infusions should be administered over 60 minutes (±15 minutes) in the absence of infusion related reactions. The line should be flushed before and after the study drug infusion. Study drug should not be administered as a bolus or a push. Seribantumab should be administered no less than 7 days after the previous dose.

5.2.4. Management of Toxicity Related to Seribantumab

5.2.4.1. Dose Limiting Toxicity

Patients will be monitored during weekly dosing for a period of 28 days (i.e., throughout C1W1, C1W2, C1W3, and C1W4) for the occurrence of DLTs. Any Grade 3 or 4 hematologic or non-hematologic toxicity considered related to seribantumab will be considered dose limiting. A DLT is defined as any AE meeting the criteria listed below, occurring during weekly treatment with seribantumab, where the relationship to seribantumab cannot be ruled out. The grading of AEs will be based on the CTCAE Version 5.0.

Hematologic toxicity

- Febrile neutropenia
- Neutropenic infection
- Grade 4 neutropenia > 7 days
- Grade ≥ 3 thrombocytopenia for > 7 days
- Grade ≥ 3 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia
- Grade ≥ 3 anemia > 7 days

Non-hematologic toxicity

- Grade ≥ 3 nausea, vomiting, or diarrhea lasting more than 72 hours despite optimal medical support with anti-emetics or anti-diarrheals
- Grade 4 (life-threatening) vomiting, or diarrhea should be considered DLTs irrespective of duration
- Any other grade ≥ 3 AE, except Grade ≥ 3 fatigue and anorexia lasting for < 7 days or Grade ≤ 2 infusion related reactions (IRR; for grade 3 or higher IRRs, seribantumab must be permanently discontinued)

Any toxicity, regardless of CTCAE grade, resulting in discontinuation or dose reduction of seribantumab treatment during the 28-day DLT evaluation period, with the exception of symptoms related to disease progression, will be considered a DLT.

All events qualifying as a DLT, regardless of seriousness, should be submitted through the defined SAE reporting requirements as described in Section 9.4 and followed through proper resolution as outlined in Section 9.5.

5.2.4.2. Management of Infusion Related Reactions

Like other IV infusions of monoclonal antibodies, seribantumab administration may be associated with IRRs. Infusion related reactions will be defined according to the National Cancer Institute CTCAE (Version 5.0) definition of an allergic reaction/infusion reaction and anaphylaxis. In past clinical studies (n=847 patients treated), IRRs with seribantumab have been rare with < 1% of patients experiencing 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, 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 over 90 minutes. In addition, for patients who experience a subsequent 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. An anti-seribantumab antibody titer should also be obtained at the resolution of the event and 28 days (± 2 days) following the event.

5.2.4.3. Toxicity Management Guidelines

When a patient experiences any Grade 3 or Grade 4 hematologic or non-hematologic toxicity, excluding infusion related reactions (Section 5.2.4.2) related to seribantumab, the following toxicity management guidelines should be followed:

Dose Interruptions and Reductions for Hematologic Toxicity

For ≥ Grade 3 hematologic toxicity, seribantumab dosing will be held until resolving to ≤ Grade 2 or the patient's baseline. Once the hematologic toxicity resolves to ≤ Grade 2 or the patient's baseline, seribantumab will be restarted at a 25% reduction of the original dose.

For recurrence of a ≥ Grade 3 hematologic toxicity, seribantumab will be held again until resolving to ≤ Grade 2 or the patient's baseline. Once the hematologic toxicity resolves to ≤ Grade 2 or the patient's baseline, seribantumab will be restarted at a 50% reduction of the original dose.

For patients who have had dose reductions of seribantumab due to hematologic toxicity, investigators may restart seribantumab at the original assigned dose, provided the toxicity has resolved to ≤ Grade 1 on the reduced dose for at least one cycle of treatment. The Investigator should consult with the Medical Monitor and Sponsor prior to any planned dose re-escalation.

Seribantumab should be permanently discontinued if the patient experiences a recurrent Grade 3 or higher treatment related hematologic toxicity, despite a 50% dose reduction.

Dose Interruptions and Reductions for Non-Hematologic Toxicity

For ≥ Grade 3 non-hematologic toxicity, seribantumab dosing will be held until resolving to ≤ Grade 1 or the patient's baseline. Once the non-hematologic toxicity resolves to ≤ Grade 1 or the patient's baseline, seribantumab will be restarted at a 25% reduction of the original dose.

For recurrence of a ≥ Grade 3 non-hematologic toxicity, seribantumab will be held again until resolving to ≤ Grade 1 or the patient's baseline. Once the non-hematologic toxicity resolves to ≤ Grade 1 or the patient's baseline, seribantumab will be restarted at a 50% reduction of the original dose.

For patients who have had dose reductions of seribantumab due to non-hematologic toxicity, investigators may restart seribantumab at the original assigned dose, provided the toxicity has resolved to ≤ Grade 1 on the reduced dose for at least one cycle of treatment. The Investigator should consult with the Medical Monitor and Sponsor prior to dose re-escalation.

Seribantumab should be permanently discontinued if the patient experiences a recurrent Grade 3 or higher treatment related non-hematologic toxicity, despite a 50% dose reduction.

Dose re-escalation is not permitted for patients who experience:

- Recurrent Grade 3 AEs determined to be clinically significant by the Investigator despite dose-reduction
- Recurrent Grade 4 AEs despite dose-reduction

Seribantumab should be permanently discontinued for patients who experience life-threatening Grade 4 AEs.

5.2.5. Potential Toxicities with Seribantumab

Overall, seribantumab has been administered IV to 869 patients in ongoing and completed studies. In the CRESTONE study, as of 08May2021, diarrhea (8 patients, 53.3%), hypokalemia (5 patients, 33.3%), and fatigue (5 patients, 33.3%) were the most commonly reported TEAEs. Grade 3 TEAEs were experienced by 3 (20.0%) patients. A total of two SAEs have been reported in one patient. Both SAEs were Grade 2, resolved, and considered not related to seribantumab. Both events were associated with the patient's concurrent illness of non-serious AE of COVID-19 infections.

For additional information on the safety associated with seribantumab as a monotherapy and in combination with standard anticancer treatments, as well as for safety observations in Investigator sponsored single patient INDs, please refer to the current version of the Investigator's Brochure.

5.3. Dose Modifications

Patients who experience a clinically significant AE (Grade ≥ 3), may have seribantumab dosing held for up to 3 weeks to allow for recovery. Upon restarting treatment with study drug, the seribantumab dose will be reduced by either 25% (first occurrence) or 50% (recurrence) per Section 5.2.4.3, as follows:

Table 3: **Dose Modification – Weekly Dosing**

Original dose level	3,000 mg
25% dose reduction	2,250 mg
50% dose reduction	1,500 mg

For patients who meet criteria to transition to Q2W dosing, please discuss with and obtain approval from the Sponsor before reducing the dose. Patients who experience clinically significant AEs

related to seribantumab during Q2W dosing must have seribantumab withheld until the AE resolves according to Section 5.2.4.3.

Seribantumab should be permanently discontinued for patients who experience life-threatening grade 4 AEs. Seribantumab should also be permanently discontinued for patients who experience clinically significant, drug-related AEs requiring a recovery period of longer than 3 weeks, unless there is compelling, objective radiological evidence of response and no alternative treatment. The Sponsor and Investigator must agree that continuation of seribantumab is in the best interest of the patient, and the patient agrees.

5.4. Study Treatment Discontinuation

A patient may withdraw from the study at any time and for any reason. Over the course of the study, the Investigator and/or Sponsor should withdraw a patient from treatment for any of the following reasons:

- Disease progression (as assessed using RECIST v1.1). Note: Patients with disease progression per RECIST v1.1 who, in both the Investigator's and Sponsor's opinions, may continue to derive clinical benefit, and who meet the criteria listed in Section 5.4.1, may be allowed to continue treatment with written approval from the Sponsor.
- Clinically significant drug-related toxicity requiring a recovery period of longer than 3 weeks, unless there is compelling, objective radiological evidence of response, no alternative treatment, and the Sponsor and Investigator agree that continuation of seribantumab is in the best interest of the patient, and the patient agrees
- Intercurrent illness compromising the ability to fulfill protocol requirements
- Requirement for alternative treatment in the opinion of the Investigator
- Significant non-compliance to protocol
- Withdrawal of consent by the patient
- Patient is lost to follow-up
- Death

When a patient is discontinued from treatment for any reason, they are to undergo the assessments in the End of Treatment visit within 4 weeks of the last dose and prior to initiating any subsequent anti-cancer therapy. All patients who discontinue treatment as a result of an adverse event (AE) must be followed until resolution or stabilization of the AE. At the time a patient withdraws from study treatment, an attempt should be made to determine the reason(s) for discontinuation.

Upon withdrawal from treatment, the patient will continue to be followed for survival and subsequent disease and treatment information every 3 months after completion of the End of Treatment visit. 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 the patient does not respond to these requests, the date of death should be captured from public records.

5.4.1. Study Treatment Beyond Progression

As noted in Section 5.4, patients with disease progression per RECIST v1.1 who, in the Investigator's and Sponsor's opinions, may continue to derive clinical benefit, may be eligible to continue in the study if they meet the criteria outlined below:

- absence of clinical symptoms or signs indicating clinically significant disease progression;
- no decline in the ECOG performance status;
- absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention;
- no significant, unacceptable, or irreversible toxicities related to the trial treatment;
- have written approval of the Sponsor;
- have signed an ICF agreeing to continue treatment; and
- no other treatment discontinuation criteria are met.

Patients must permanently discontinue seribantumab treatment if subsequent imaging demonstrates further disease progression of ≥ 10% in the target lesions, unequivocal or further progression in non-target lesions, and/or the appearance of new lesions.

5.5. Concomitant and Prohibited Therapies

Standard supportive medications may be used in accordance with institutional guidelines and Investigator discretion. These may include hematopoietic growth factors to treat neutropenia, thrombocytopenia or anemia in accordance with American Society of Clinical Oncology (ASCO) Guidelines (but not for prophylaxis in Cycle 1), transfusions, anti-emetics, anti-diarrheals, antibiotics, antipyretics, and corticosteroids (up to 10 mg per day prednisone or equivalent, unless a compelling clinical rationale for a higher dose is articulated by the Investigator and approved by the Sponsor; permitted corticosteroid uses include topical/cutaneous, ophthalmic, nasal and inhalational steroids, as well as short courses to treat asthma, chronic obstructive pulmonary disease, or other non-cancer related conditions).

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 study treatment initiation and the study treatment discontinuation visit. After the End of Treatment Visit, only anti-cancer therapies will be collected in addition to survival information.

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 gonadotropin-releasing hormone analogues for more than 90 days prior to study entry may continue while on study)

- Any other investigational therapy

5.5.1. Concurrent Palliative Radiotherapy and Elective Procedures

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. Seribantumab treatment should be interrupted during palliative radiotherapy, stopping 3 days before and resuming treatment no earlier than 1 day thereafter. In general, target lesions being used to measure response should not be irradiated without discussion with the Sponsor and may be reason for the patient to be removed from study for progressive disease. Irradiated lesions will be considered not evaluable for response but can still be used to assess disease progression. The intensities, number, and dates of doses received for allowed palliative radiotherapy should be recorded on the appropriate eCRF.

Although seribantumab is not expected to significantly affect wound healing, any unusual findings should be recorded as potential AEs. In the event elective procedures, including surgery, are necessary during study participation, seribantumab dosing should be stopped 3 days before surgery and resumed no sooner than 24 hours after surgery.

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

6.1. COVID-19 Public Health Emergency Impact on Protocol Assessments

During study conduct, challenges may arise, for example, from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product, or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering the study drug or adhering to protocol-mandated visits and laboratory/diagnostic testing. During the course of study conduct, protocol modifications may be required, and there may be unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 public health control measures. In such case, these incidences should be documented in the study case report form(s).

Since study participants may potentially not be able to come to the investigational site for protocol specified visits, alternative methods for safety and efficacy assessments (e.g., phone contact, virtual visit, telemedicine, visiting nurse to patient's residence, alternative location for assessment, including local labs or imaging centers) could be implemented when necessary and feasible, and would be sufficient to assure the safety of study participants.

6.2. Schedule of Assessments

The study schedule of events can be found in Table 4. Detailed information of study assessments is provided in Section 7.

Table 4: Schedule of Assessments

Evaluation / Procedure **Visit Window**	**Screening** **(D-28 to 0)**	**Treatment** **Evaluations/Procedures +/-2 days** **Seribantumab Dosing +2 days**	**End of Treatment Visit (EOT)[13]** **± 3 days**	**Survival Follow-Up Every 3 months after EOT[15]** **± 1 month**
Informed consent	X			
Medical, surgical, malignancy history	X			
Archived tumor tissue or fresh biopsy	X		X[14]	
Urine or serum pregnancy test	X	Every 28 days	X	
Physical Exam and ECOG PS[1]	X	Weekly during C1, then at W1 of every Cycle thereafter	X	
Vital signs	X[8]	X	X	
CBC	X[2,8]	Weekly during C1, then every 14 days starting C2W1 then every 28 days starting after 1 year on treatment	X	
Serum chemistry	X[3,8]		X	
Blood sample(s) for PK[4]		C1W1, C1W3, C2W1, C2W3, C3W1, C3W3, C4W1, C5W1, C6W1, and then every even Cycle beginning with C8W1		
12-lead ECG	X[5]		X[5]	
Serum for anti-seribantumab immunogenicity[6]		C1W1, C1W3, C2W1, C2W3, C3W1 and C3W3, C4W1, C5W1, C6W1, and then every even Cycle beginning with C8W1	X[6]	
Whole blood for cfDNA[7]		C1W1 and C2W1	X	
Concomitant meds[8]	X	X	X	
Seribantumab dosing[9]		X		
AE/SAE assessment and reporting[10]	X			
Quality of Life Questionnaire (EORTC QLQ-C30)		C1W1, and at W1 of every other Cycle[16]	X	
Disease evaluation	X[11]	Week 6, Week 12, Week 18, Week 24; then every 8 weeks (through Week 48); then every 12 weeks (beginning at Week 60)	X[12]	
Overall Survival Reporting[15]				X

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen, C = cycle; CBC = complete blood count; cfDNA = cell free DNA; CT = computerized tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = end of infusion; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life

Questionnaire-Core 30; EOT = end of treatment; GI = gastrointestinal; HEENT = head, eyes, ears, nose, and throat; Ig = immunoglobulin; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; RBC = red blood cell; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; W = week; WBC = white blood cell

[1] Review of systems: HEENT, extremities, GI/abdomen, lymph nodes, musculoskeletal, respiratory/pulmonary, and skin, body weight, and height during Screening. Symptom-directed physical and neurological examinations, including measurement of weight, may be performed at other time points. After screening, physical exams should occur weekly during Cycle 1 and at Week 1 of every cycle thereafter.

[2] Hemoglobin, hematocrit, RBC count, WBC count with differential (neutrophils [count and percent] and lymphocytes, monocytes, eosinophils, basophils [percent], and platelet count). Samples collected for Screening may be used for C1W1 if collection occurs within 2 days of the C1W1 visit. Ad hoc samples may be requested by the Sponsor or at the investigator's discretion.

[3] Serum or plasma chemistries (non-fasting), including alkaline phosphatase, albumin, ALT, AST, blood urea nitrogen (BUN), cholesterol, creatinine, glucose, LDH, uric acid, total and direct bilirubin, total protein, sodium, potassium, calcium, chloride, bicarbonate, magnesium and phosphate. Samples collected for Screening may be used for C1W1 if collection occurs within 2 days of the C1W1 visit. Ad hoc samples may be requested by the Sponsor or at the investigator's discretion.

[4] Seribantumab PK sampling: At C1W1 sampling should occur immediately prior to dosing, at the end of infusion (EOI) and 1 hour after EOI. At C1W3, C2W1, C2W3, C3W1, C3W3, C4W1, C5W1, C6W1, and then every even Cycle beginning with C8W1: Samples should be collected immediately prior to each dose and at the EOI. Sampling should occur within 15 minutes of starting or completing the seribantumab infusion. Ad hoc PK samples may be requested by the Sponsor.

[5] Screening electrocardiogram (ECG) should be performed in triplicate. End of Treatment (EOT) ECG reading should be repeated only if the initial reading at the EOT visit showed treatment emergent abnormalities. Ad hoc ECGs may be requested by the Sponsor.

[6] Anti-seribantumab immunogenicity samples should be collected prior to dosing at scheduled time points. Should a patient experience an infusion reaction on study, an anti-seribantumab antibody assay will be taken within 24 hours of the event. 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, upon resolution and 28 days (± 2 days) following the event.

[7] Whole blood for cfDNA analysis should be obtained prior to treatment on C1W1 and C2W1. Whole blood for cfDNA analysis should be obtained at the EOT visit even if radiographic disease assessment is not performed. Whole blood for cfDNA analysis should only be collected at subsequent visits if it was collected prior to treatment at C1W1.

[8] Performed prior to seribantumab administration.

[9] Seribantumab dosing will consist of weekly 1-h infusions until study treatment discontinuation criteria are met. Seribantumab doses should be administered no less than 7 days apart.

[10] All AEs and SAEs are collected and reported from the time of informed consent through the EOT visit or 28 days after last dose, whichever occurs later.

[11] Baseline Disease Assessment: Radiographic tumor measurements using CT (computerized tomography) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis, with additional regions affected by disease as appropriate, and CT or MRI of brain (for patients with suspected brain involvement or a history of brain metastases) within 28 days of seribantumab dosing (first dose). Contrast should be utilized (excluding CT of the chest) unless there is a clear contraindication (e.g., decreased renal function or allergy that cannot be addressed with standard prophylactic treatments). Disease assessments will utilize RECIST v1.1. Disease assessments will occur prior to seribantumab administration on dosing days and occur within a ± 14-day window. Refer to Section 7.7 for details on confirmation of response.

[12] All patients that come off treatment for reasons other than progressive disease will have a disease assessment performed at the EOT visit.

[13] End of Treatment visit should be completed within 4 weeks of the last dose of study drug administration.

[14] An optional fresh tumor biopsy will be performed at the time of progression and prior to the completion of the EOT assessments if feasible to evaluate potential patterns of resistance to seribantumab.

[15] Every survival follow-up should include collection of any new anti-cancer therapies and procedures taken after EOT visit. Should patients refuse or drop out of survival follow-up, attempts should be made to obtain any death information available via public records.

[16] European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) should be conducted prior to dosing at C1W1 and at W1 of every other cycle thereafter, i.e., C3W1, C5W1, etc. The questionnaires should be answered by the patient to the best of his/her ability, preferably prior to learning the results of the radiologic disease assessment. QOLs should only be performed at subsequent visits if they were performed prior to dosing at C1W1.

6.3. Screening and Baseline Visit

All procedures for screening and baseline are outlined in Section 6.2. Patients who screen fail can be rescreened. Rescreened patients will be provided a new patient identification number.

In discussion with the Sponsor, if a patient is identified who does not have access to local NRG1 fusion testing, the Sponsor may offer support for testing of enriched patient population as a pre-screening procedure. Enriched patient population may include patients diagnosed with KRAS wild-type IMA, and KRAS wild-type pancreatic ductal adenocarcinoma (PDAC). Additional tumor types of interest may be added at the Sponsor's discretion. For patients diagnosed with IMA or PDAC who have not been screened for KRAS status, the Sponsor may provide access to KRAS testing under the pre-screening mechanism. The Sponsor may also support testing for patients with other tumor types who have exhausted all other options for treatment. For further descriptions of the clinical and laboratory assessments required, please refer to Section 7 and Section 8, respectively.

6.4. On-Study Visits

Patients who are confirmed to meet all inclusion and exclusion criteria will be assigned to the appropriate treatment cohort based upon prior treatment history. Treatment must be initiated within 7 days of Enrollment and Cohort Assignment.

All on-study procedures and assessments are outlined in Section 6.2.

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 4 weeks of last dose of study drug and prior to the initiation of any subsequent anticancer therapy. All End of Treatment procedures and assessments are outlined in Section 6.2.

6.6. Survival Follow-up

Survival data will be collected via written communication (e.g., telephone, email, electronic medical record) or clinic visits every 3 months (±28 days) from the date of last treatment 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 during every survival follow-up. 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 of the following clinical procedures should be performed in accordance with the schedule of assessments outline in Section 6.2.

7.1. Medical History and Demographics

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

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 AEs. 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 collected and reported throughout the course of the study, from the time of informed consent through the end of treatment (EOT) visit or 28 days after the last dose of seribantumab, whichever occurs later, and followed through to resolution as detailed in Section 9.

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

7.3. Physical Examination and Performance Status Assessment

Physical examination will include a review of systems: head, eyes, ears, nose, and throat, extremities, GI/abdomen, lymph nodes, musculoskeletal, respiratory/pulmonary, and skin, body weight, and height during Screening. Symptom-directed physical and neurological examinations, including measurement of weight, may be performed at other time points. The ECOG performance status will be obtained by the Investigator or his/her designee by questioning the patient about their functional capabilities.

7.4. Vital Signs

Vital signs will be collected at Screening and prior to seribantumab administration at dosing visits and should include resting blood pressure, pulse, respiratory rate, and temperature.

7.5. Electrocardiogram

A 12-lead electrocardiogram (ECG) will include a description of the cardiac rate, rhythm, interval durations, and an overall impression. The corrected QT interval (QTc) should be calculated using the Fridericia method (QTcF).

7.6. Collection of Quality of Life (EORTC QLQ-C30) Questionnaire

The EORTC QLQ-C30 should begin to be implemented for newly enrolled patients when available. Only patients who have completed questionnaires at baseline (prior to dosing at C1W1) should complete subsequent questionnaires at the follow up periods.

7.7. Disease Evaluation

Tumor response will be evaluated by the local radiologist according to the RECIST v1.1 (Eisenhauer et al., 2009) to establish disease progression by computerized tomography (CT) or magnetic resonance imaging (MRI) of chest, abdomen, and pelvis at minimum, and in additional regions such as head, neck, or extremities, as appropriate if disease or symptoms are present. Patients enrolled with a history of central nervous system (CNS) metastases should additionally have a head CT/MRI scan with contrast performed at each tumor assessment. 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. Independent retrospective central reviews of all scans may be conducted in addition to review performed by the local radiologist. 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 PR or CR, changes in tumor measurements must be confirmed by repeated assessments that should be performed ≥ 28 days after the criteria for response are first met.

Patients that discontinue study drug administration for reasons other than progressive disease including due to toxicities will continue to receive tumor assessments beginning at weeks 6, 12, 18 and 24 with a ± 2-week window and subsequently every 8 weeks (± 2 weeks) through Week 48, followed by every 12 weeks (± 2 weeks) beginning at Week 60 until disease progression and evaluated using the RECIST guidelines (version 1.1). Patients will be evaluated until disease progression, initiation of next anti-cancer therapy, death, or withdrawal of consent.

7.7.1. Independent Central Review of Scans

All treatment decisions will be made by the Investigator using local assessments. All images should be submitted to a central imaging facility and may be analyzed centrally by independent reviewers in accordance with the Imaging Charter. Please refer to the image acquisition guidelines for details on how images must be acquired and how scanners must be qualified. In addition, bone scans, x-rays, cytologic data (e.g., relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid, etc.), and relevant clinical information including medical photography will be forwarded to the review facility to aid in the tumor response assessment. Full details are listed in the Imaging Charter.

NOTE: Data from the independent review of tumor measurements will not be sent back to investigators.

8. LABORATORY PROCEDURES AND ASSESSMENTS

8.1. Complete Blood Count

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

8.2. Serum Chemistry

Serum or plasma chemistry (non-fasting) will include electrolytes (sodium, potassium, calcium, chloride, bicarbonate, magnesium, and phosphate), blood urea nitrogen, serum creatinine, cholesterol, glucose, total and direct bilirubin, AST, ALT, alkaline phosphatase, lactate dehydrogenase, uric acid, total protein, and albumin.

8.3. 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.

8.4. Pharmacokinetic Testing

8.4.1. Seribantumab PK samples

Plasma samples will be obtained from patients as outlined in Section 6.2. A laboratory manual will be provided with instructions for collecting, processing, and shipping these samples.

8.5. Anti-seribantumab Immunogenicity

Serum samples will be collected prior to dosing at the scheduled time points outlined in Section 6.2 to determine the presence of an immunologic reaction to seribantumab (i.e., human anti-human antibodies; HAHA) and for any patients who experience a Grade 3 or higher infusion reaction during seribantumab administration. A laboratory manual will be provided with instructions for collecting, processing, and shipping these samples.

8.6. Biomarker Samples

Biomarker data will be explored from collected tissue (prior to treatment and at the EOT visit for those patients who undergo an optional biopsy). Additionally, for patients with tumors where collection of tumor markers is clinically relevant (i.e., pancreas cancer, breast cancer, etc.), tumor marker values will be collected in the eCRF if they are collected. Efficacy outcomes considered for pre-specified mechanistic biomarker analysis will include but not be limited to OS, PFS, and ORR.

8.6.1. Archived Tumor Sample / Tumor Biopsy

If archived tumor tissue is available, it should be submitted in lieu of obtaining a fresh tumor biopsy for central confirmation of NRG1 gene fusion status at the time of study enrollment for patients assigned to Cohort 1. For patients where adequate archival tissue is not available, tumor biopsy procedures performed on an outpatient basis and associated with a low risk of major complications, per the recent guidance from ASCO (Levit et al. 2019), may be considered by the treating physician, in accordance with site specific consent and standard procedures. Refer to the lab manual for additional details about tissue collection requirements.

Central confirmation of NRG1 gene fusion status will be performed on a retrospective basis by Caris Life Sciences, utilizing their RNA-based NGS test, MI Transcriptome™. Patients are enrolled

and treated based on local NRG1 fusion testing results. Immediately following enrollment, Investigators and study staff will be required to obtain, process and ship the required archival tumor tissue for central confirmatory testing. A minimum of 55 patients with centrally confirmed NRG1 gene fusion positive tumors based on an RNA-based NGS testing method will be enrolled into Cohort 1.

If central laboratory testing fails to confirm the presence of an NRG1 fusion, or insufficient tumor tissue is provided for central testing after enrollment, patients would be permitted to continue participating in the study at the Investigator's discretion, as long as they do not meet criteria for treatment discontinuation in Section 1.1.

Additional directions regarding processing and shipping archival or fresh tissue samples for central confirmatory testing (Cohort 1 only), or fresh tissue samples obtained at the time of tumor progression (optional biopsy), will be outlined in the laboratory manual.

8.6.2. Whole Blood for cell free DNA

Whole blood samples will be collected prior to dosing at time points described in Section 6.2. 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 NRG1 fusion positive advanced solid tumor patients. If there is remaining sample available after conducting these analyses, it will be used by the Sponsor for future analysis of biomarkers that may be mechanistically linked to seribantumab activity. At the time of informed consent, patients will be able to refuse storage of these remaining samples.

Directions for processing and shipping the samples will be outlined in the laboratory manual.

9. ADVERSE EVENTS AND REPORTING

9.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and does not necessarily have to have a causal relationship with this treatment. An AE 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 investigational product.

All AEs, complaints, or symptoms that occur from the time that written informed consent has been obtained through the EOT Visit or 28 days after the last dose of seribantumab, whichever occurs later, are to be recorded on the appropriate eCRF (events that occur prior to first dose of study drug are considered medical history, events that occur on or after the first dose of study drug are considered TEAEs). Documentation must be supported by an entry in the patient's source medical records. Clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected during the study, or are present at Screening and significantly worsen during the study, should be reported as AEs. Each AE is to be evaluated for duration, severity, and causal relationship with the investigational product, underlying disease or other factors.

Worsening of a pre-existing medical condition, (i.e., diabetes, migraine headaches) should be considered an AE if there is either an increase in severity, frequency, or duration of the condition

or an association with significantly worse outcomes. Disease progression in and of itself is not considered an AE or SAE. Events attributed to disease progression should be reported as an SAE if they meet any of the SAE reporting criteria listed in Section 9.4.

Interventions for pretreatment conditions (i.e., elective cosmetic surgery) or medical procedures that were planned prior to study enrollment are not considered AEs.

For an AE leading to death, the outcome should be recorded with the event causing death. AEs that are ongoing at the end of study or time of death are to be noted as "continuing". Classification of AEs is to be done by the Investigator in accordance with the NCI CTCAE Version 5.0.

The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an AE.

9.2. Grading and Intensity of Adverse Events

Each AE will be graded according to the NCI CTCAE Version 5.0, which may be found at http://ctep.cancer.gov/reporting/ctc.html. 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/Grade 1:** an event not resulting in disability or incapacity and which resolves without intervention;
- **Moderate/Grade 2:** an event not resulting in disability or incapacity, but which requires intervention;
- **Severe/Grade 3:** an event resulting in temporary disability or incapacity and which requires intervention;
- **Life-threatening/Grade 4:** an event in which the patient was at risk of death at the time of the event;
- **Fatal/Grade 5:** an event that results in the death of the patient.

9.3. Relationship to Study Drug

The Investigator must attempt to determine if there exists reasonable possibility that an AE is related to the use of the study drug, according to the following guidelines:

The Investigator will categorize each AE as to its potential relationship to study drug using the categories of Yes (causally related) and No (unrelated) as defined below. The assessment of the relationship of an AE to the administration of study drug is a clinical decision based on all available information at the time.

No:

The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship, while another cause (e.g., concomitant medications, comorbidities, disease progression or complications, etc.) is suspected.

Yes:

The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (e.g., concomitant medications, comorbidities, disease progression or complications, etc.) can be identified.

The following factors should also be considered when the Investigator categorizes each AE:

- Temporal sequence from treatment
- Underlying, concomitant, or intercurrent diseases
- Concomitant medications
- Clinical and/or nonclinical data regarding whether a particular AE is a class effect
- Pharmacology and PK for the study drug

9.4. Serious Adverse Event Reporting

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event

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.

All SAEs occurring from the time that written informed consent has been obtained through the EOT Follow-up Visit (within 28 days after the last dose of study drug administration) must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence. All SAEs that the Investigator considers related to study drug occurring after the 28-day follow-up period must be reported to the Sponsor.

Elective admissions to the hospital for procedures which were planned prior to entering the trial are not SAEs. However, if hospitalization is prolonged for any reason, an SAE form must be completed.

An event attributed to disease progression must be reported as an SAE if it meets any of the SAE reporting criteria listed in this section. If death due to disease progression occurs within 28 days

after the last dose of study drug, the event term should be listed as "malignant neoplasm progression" with the outcome of death.

To report the SAE, complete the SAE form electronically in the EDC system for the study. When the form is completed, Medpace Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the internet, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE hotline (phone number listed below), and fax the completed paper SAE form to Medpace (fax number below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information

Medpace Clinical Safety
Medpace SAE Hotline
Telephone: +1-800-730-5779, dial "3" or +1-513-579-9911, dial "3"
Fax: +1-866-336-5320 or +1-513-579-0444
Email: medpace-safetynotification@medpace.com

The Investigator will be requested to supply detailed information regarding the event. SAEs must also be reported to the Institutional Review Board (IRB) and a copy of that report must be retained at the investigative site and filed in the Investigator Site File in accordance with the requirements of that institution.

Although not considered an AE per se, the Sponsor must be notified of any patient or patient's partner who becomes pregnant during a clinical study according to Section 9.6.

9.5. Serious Adverse Event Follow-up

For all SAEs occurring during the study, the Investigator must submit follow-up reports to the Sponsor regarding the status of the SAE and the patient's subsequent course until the SAE has resolved, or until the condition stabilizes or is deemed chronic (in the case of persistent impairment), or the patient dies.

AEs, excluding AEs due to disease progression, that lead to permanent discontinuation of the study drug will be followed until resolution to baseline, the condition stabilizes or is deemed chronic, withdrawal of consent, or death.

9.6. Pregnancy Reporting

If the patient or partner of a patient participating in the study becomes pregnant while on study, the Investigator should report the pregnancy to the Sponsor's clinical safety representative within 24 hours of being notified. The Sponsor's safety representative will then forward the Pregnancy form to the Investigator for completion as outlined in the Study Manual.

A patient becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed. 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. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. The Sponsor will collect information on the outcome of the pregnancy. If the outcome of the pregnancy meets the

criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

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

A full Statistical Analysis Plan (SAP) will provide detailed methodology for summary and statistical analyses of the data collected in this study.

10.1. Study Endpoints

Primary

- Objective response rate as assessed by independent radiologic review according to RECIST v1.1

Secondary

- Duration of Response by independent radiologic review
- ORR and DoR by investigator assessment
- Progression-free Survival by independent radiologic review and investigator assessment
- Overall Survival
- Clinical Benefit Rate (CR, PR, SD ≥ 24 weeks) by independent radiologic review and investigator assessment
- Safety of seribantumab

Exploratory

- PK parameters following weekly, Q2W, and Q3W dosing
- To explore the association between mechanistically linked biomarkers and clinical outcomes
- Changes from baseline in quality of life, as measured by the EORTC QLQ-C30

10.2. Analysis Populations

All efficacy analyses will be performed by cohort. Analyses for the Cohort 1 primary efficacy analysis population will be intended to support a potential registration. Analyses for Cohort 2 and Cohort 3 efficacy analysis population will be exploratory.

10.2.1. Cohort 1 Primary Efficacy Analysis Population

The population will be used for the primary analysis of efficacy for registration purpose. It will include Cohort 1 patients enrolled in this study who meet all criteria listed below:

- centrally confirmed NRG1 gene fusion
- received at least one dose of seribantumab at 3,000mg QW dosing regimen (starting with Protocol Version 3.0 and later). Patients in the safety-run in (enrolled under Protocol Version 2.0 or earlier) will be included if they received seribantumab at 3,000 mg QW beyond induction/re-induction
- received at least one prior standard therapy in the locally advanced or metastatic setting
- at least one measurable lesion at baseline as assessed per RECIST v1.1 based on independent central reviews

10.2.2. Cohort 2 and Cohort 3 Efficacy Analysis Population

These populations will be used for exploratory efficacy analysis for each cohort, respectively. All patients enrolled in each cohort who received at least one dose of seribantumab and had at least one measurable lesion at baseline assessed per RECIST 1.1 based on investigator assessments will be included in the analysis. With the release of Protocol Version 5.0, Cohort 3 was closed to enrollment. Under Protocol Version 5.0/Protocol Administrative Letter 8.0, Cohort 2 was closed to enrollment.

10.2.3. Safety Analysis Population

The safety analysis population includes patients receiving at least one dose of seribantumab therapy across any of the three treatment cohorts (e.g., Cohort 1, 2, and 3) and across any of the seribantumab dosing regimens. The safety population will be used for the overall safety analysis.

10.3. Determination of Sample Size

At least 55 patients with centrally confirmed NRG1 gene fusion positive cancer will be enrolled in the Cohort 1 primary analysis population as defined in Section 10.2.1. This sample size will provide approximately 90% power for the lower bound of the 95% CI to exclude 20% assuming the ORR is 40% with seribantumab treatment.

With the release of Protocol Version 5.0, Cohort 3 was closed to enrollment. Under Protocol Version 5.0/Protocol Administrative Letter 8.0, Cohort 2 was closed to enrollment.

10.4. Statistical Considerations

Categorical variables will be summarized by frequency distributions (number and percentages of patients) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, maximum).

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.

Due to the ongoing COVID-19 pandemic, additional analyses (e.g., sensitivity analysis) will be performed to assess the impact of COVID-19 on clinical study data. Documentation for reasons for failing to obtain a protocol specified assessment and/or alternative procedures used to collect safety and efficacy data will be required. Further details regarding these planned analyses will be described in the Statistical Analysis Plan.

Data collected from patients enrolled in Australia (MoST/CRESTONE subset) will contribute to a separate subgroup analysis in addition to the analyses described below. Further details on the MoST/CRESTONE subset can be found in Appendix B.

10.5. Efficacy Analysis

10.5.1. Primary Efficacy Endpoint for Cohort 1

Objective response rate (ORR) is the primary efficacy endpoint and will be analyzed based on the Cohort 1 primary efficacy analysis population.

ORR is determined by RECIST v1.1 (confirmed CR+PR) and will be assessed by independent radiographic review. To be assigned a status of confirmed PR or CR, changes in tumor measurements must be confirmed by repeated assessments at least 4 weeks (28 days) after the criteria for response are first met. Tumor assessments after the initiation of new anticancer therapy should not be used to derive the ORR. The point estimate of the ORR along with the 2-sided 95% exact Clopper-Pearson CI will be presented.

ORR will also be assessed by subgroups defined by the predefined factors listed in Section 10.8.

10.5.2. Secondary Efficacy Endpoints for Cohort 1

Secondary efficacy endpoints will be analyzed based on the Cohort 1 primary efficacy analysis population.

Objective Response Rate (ORR): ORR based on the investigator assessments will be analyzed similarly as described for the primary efficacy analysis (Section 10.5). This is considered a sensitivity analysis.

Duration of Response (DoR): Duration of response is based on independent radiographic review. For patients who achieve a confirmed CR or PR, DoR is defined as the number of months from the start date of CR or PR (whichever response status is observed first and subsequently confirmed), to the date of first documented radiographical progression of disease using RECIST v1.1, or death from any cause, whichever comes first. DoR will be calculated for patients who are responders, i.e., those who achieve a confirmed CR or PR. The initiation of new anticancer therapy will mean the end of the response for the calculation of DoR. Responders who have not experienced disease progression, death, or new anticancer therapy at the time of the analysis will be censored at the date of the last tumor assessment. If no tumor assessments are available after the date of the first occurrence of response, the patient will be censored on the date of the first occurrence of the response. DoR will be estimated using the Kaplan-Meier method. The median DoR and the proportion of responders with durable responses at 6 months or 12 months will be estimated along with 95% CI.

DoR by investigators: DoR based on the investigator assessments will be analyzed similarly as described for the respective endpoint based on the independent radiographic reviews. This is considered a sensitivity analysis.

Progression-free Survival (PFS): PFS is defined as the time from the date of seribantumab treatment initiation (Dose 1) to the first documented radiographical progression of disease using RECIST v1.1, or death from any cause, whichever comes first. The Kaplan-Meier method will be used to estimate PFS. In addition to the Kaplan-Meier plot of PFS, the median PFS time, 6-month, and 12-month PFS rates will be estimated along with 95% CI. PFS analysis will be performed separately based on central radiographic review and investigator assessments. Additional sensitivity analysis of PFS may be performed using different censoring rules. These sensitivity analyses will be detailed in the SAP.

Overall Survival: OS is defined as the time from the date of treatment seribantumab treatment initiation (Dose 1) to the date of death from any cause. The Kaplan-Meier method will be used to estimate OS. In addition to the Kaplan-Meier plot of OS, the median OS time, 6-month, and 12-month survival rates will be estimated, along with 95% CI.

Clinical Benefit Rate (CBR): Clinical benefit rate is defined as the proportion of patients who achieve PR, CR, or SD which is maintained through at least 24 weeks per RECIST v1.1. Tumor assessments after the initiation of new anticancer therapy should not be used to derive the CBR. Patients with no baseline disease assessment or no evaluable post-baseline disease assessments (i.e., NE) or with ongoing SD but short of 24 weeks at the time of analysis will be considered as not having attained clinical benefit and included in the denominator in the calculation of the CBR. CBR will be summarized similarly as the ORR with both point estimate and 95% Clopper-Pearson CI provided. CBR analysis will be performed separately based on central radiographic review and investigator assessments.

Secondary efficacy endpoints will also be assessed by subgroups defined by the predefined factors listed in Section 10.8.

10.5.3. Exploratory Efficacy Analysis for Cohorts 2 and 3

Efficacy analyses of the primary efficacy endpoint and secondary efficacy endpoints for Cohorts 2 and 3 will be performed separately using the same methods described above. For the ORR, DoR, CBR, and PFS endpoints, investigator assessments will be used.

10.6. Safety Analysis

Safety analyses (AE and laboratory analyses) will be performed using the safety analysis population. Adverse events will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Severity will be graded according to the NCI CTCAE Version 5.0.

Treatment-emergent adverse events (TEAEs), TEAE grade 3 and higher, TEAE-related, SAEs, and discontinuation due to AE will be reported by frequency and percent summaries. Adverse events will be summarized by System Organ Class and preferred term. All AE data will be listed by patient.

Treatment-emergent adverse events 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. Treatment-emergent adverse events will be collected through the end of treatment visit.

Laboratory, vital signs, and ECG data will be summarized according to parameter type.

A SRC has been established to assess the safety, tolerability, and PK exposure (if available) of seribantumab. Refer to Section 3.2 and the SRC Charter for further details.

10.7. Interim Analysis

A pre-planned interim analysis based on investigator assessed ORR will be conducted after 20 patients are enrolled and treated in the Cohort 1 and followed for at least one post-baseline tumor assessment with sufficient follow-up (at least one post-baseline tumor assessment [i.e., 6 weeks ± 2 weeks]). Should four or more objective responses be observed at the time of the interim analysis, enrollment to Cohort 1 for the primary analysis population will continue until a minimum of 55 patients with centrally confirmed NRG1 gene fusion positive cancer. The futility analysis will be considered non-binding as factors other than ORR may be factored in (such as depth of response, duration of response, tumor type, and fusion partner).

An expanded SRC will be established to evaluate the interim futility analysis in addition to safety as detailed in Section 3.3.

10.8. Covariates and Subgroups

Predefined covariates and subgroups include:

- Age, age groups (< 65, ≥ 65 years)
- Gender
- Geographic region (US vs non-US)
- Tumor type
- Fusion partner
- Number and/or type of ERBB-directed therapy in cohort 2
  - 1 versus >1
  - TKI versus monoclonal antibody

Efficacy and safety analyses based on the subgroups may be performed as appropriate.

10.9. Pharmacokinetic Analysis

Plasma concentrations by patient, cycle, day, and time will be obtained and documented at various time points during treatment with seribantumab (refer to Section 6.2).

10.10. Exploratory Analysis

Biomarker analyses will include summary of the biomarker of interest based on the biomarker analysis population. Additional analyses correlating biomarkers with efficacy and safety endpoints may be performed.

Changes from baseline in quality of life, as measured by the EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30) will be summarized and plotted by visit.

11. STUDY ADMINISTRATION

11.1. Pre-Study Documentation

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

- A signed FDA Form 1572 or equivalent document
- A current (i.e., updated no more than 24 months prior) curriculum vitae for the Investigator and each sub-investigator listed on the FDA Form 1572 or equivalent document that is signed and dated.
- A copy of the current medical license for the Investigator and each sub-investigator.
- A letter from the IRB/Ethics Committee (EC) stipulating approval of the protocol, the informed consent document, and any other material provided to potential study participants with information about the study (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

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 study. 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 SAEs will be de-identified to preserve confidentiality.

11.3. Study 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 studies.

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 in addition to a sample pre-screening consent that includes all the requirements for informed consent according to the ICH Good Clinical Practice (GCP), U.S. FDA guidelines (21 CFR 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 study, and each prospective participant must be given adequate time to discuss the study with the Investigator or site staff and to decide whether or not to participate. Each patient who agrees to participate in the study 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 study 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 study 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 study. 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 study 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 study at the conclusion of the study.

11.6. Monitoring

Overall study monitoring will be conducted through a combination of on-site visit and centralized monitoring. A clinical monitor will make regularly scheduled trips to the investigational site to review the progress of the study, study data and site processes. At each visit, the monitor will review various aspects of the study including, but not limited to: screening and enrollment logs; compliance with the protocol and study manuals 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 Elevation Oncology, 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 eCRFs 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 study, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other study-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 study-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 other regulatory agencies may review the conduct or results of the study at the investigational site. The investigator must promptly inform Elevation Oncology of any audit requests by health authorities and will provide Elevation Oncology 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 study 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 study patient. All patients in the study will be identified by a unique identifier which will be used on all eCRFs 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 study.

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 will 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 and companion diagnostic 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 patients.

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 study 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 study (including, but not necessarily limited to, eCRFs, 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 other regulatory authorities

The Sponsor will promptly inform all investigators and the FDA and/or other 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 Date

Valerie Jansen, MD, PhD
Chief Medical Officer
Elevation Oncology, Inc.
888 Seventh Avenue, 12th Floor
New York, NY 10106

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APPENDIX A: PREVIOUS CRESTONE DOSING SCHEDULES

Prior to IRB/IEC approval for Protocol Version 4.0, treatment for all eligible patients consisted of initial Induction (once weekly dosing x 4 weeks) followed by Q2W maintenance dosing with seribantumab. (Note: Despite the provision to switch to Q3W dosing under Protocol Version 2.0, no patients enrolled to study ever received Q3W seribantumab treatment.)

The pharmacokinetics of seribantumab were quantified by the former Sponsor across multiple phase 1 and 2 studies (n=499) using mixed-effect modeling. The majority of these studies utilized the 40/20 mg/kg weekly dosing regimen in combination with other anticancer therapies. Overall, the final best-fit model was a two-compartment model with association between (sex, weight) and central clearance. The terminal half-life was determined to be approximately 100 hours and achievement of steady state occurred after 3-4 repeat doses, as had been described from the initial phase 1 monotherapy experience in 43 patients.

In addition, the former Sponsor conducted dose simulation studies based upon population PK to assess weight-based versus fixed dosing. These dose simulation studies confirmed similar exposure (C_{max}) would be expected between the 40 mg/kg and 3,000 mg fixed-dose, as well as the 20 mg/kg and a 1,500 mg fixed-dose in average weight patients. The estimated mean C_{max} levels were approximately 1000 mg/L and the estimated steady state (C_{avg}) levels were approximately 600 mg/L with the 40/20 mg/kg weekly dosing regimen. Notably, in a combination study (Study MM-121-01-101) with weekly administration of seribantumab and daily erlotinib in an EGFR wild-type NSCLC population (e.g., a non-NRG1 fusion population), the achievement of seribantumab average concentrations ≥ 500 mg/L appeared to be associated with improved efficacy.

Given that the NRG1 fusion patients to be enrolled in the CRESTONE study are expected to be heavily pretreated, metastatic patients who have exhausted standard treatment options, the initial dosing regimen was designed to deliver rapid steady state levels with a 4-week induction phase consisting of once weekly dosing. This induction treatment course was to be followed by a consolidation (3,000mg IV Q2W x 6 doses) and maintenance (3,000 mg IV Q3W) phase of dosing, in the initially approved Protocol Version 2.0. These subsequent dosing phases were expected to be well tolerated, and they were based on previously defined thresholds (e.g., > 100 mg/L minimum and ≥ 500 mg/L average serum concentrations), which were established in non-NRG1 fusion positive cancer models and patients, which may not be relevant to tumors harboring oncogenic NRG1 gene fusions.

Further PK modeling (Data on file, Feb 2020; NCR001-01 PK Report) was performed prior to the initiation of the CRESTONE study to support the initial planned weekly induction dosing regimens (e.g., Induction Regimen 1: 3,000 mg IV week 1 followed by 2,000 mg IV weeks 2, 3 and 4; and Induction Regimen 2: 3,000 mg IV once weekly x 4 doses). The results from this initial PK modeling (Data on file, Feb 2020; NCR001-01 PK Report) indicated the range of predicted C_{max} and C_{avg} values with Induction Regimen 1 would be comparable to levels observed in patients treated with the 40/20 mg/kg weekly dosing regimen from the initial monotherapy study (MM-121-01-100 study), while Induction Regimen 2 would increase exposure during the initial 4 weeks by approximately 60% compared to the previously studied 40/20 weekly regimen.

Prior Induction Regimens

Induction Regimen 1: Seribantumab 3,000 mg 1-h IV as a loading dose at the C1W1 visit, followed by 2,000 mg 1-h IV once weekly at C1W2, C1W3 and C1W4.There were no DLTs observed with Induction Regimen 1. Upon review and recommendation by the SRC, the next 6 patients enrolled and initiated treatment with Induction Regimen 2.

Induction Regimen 2: Seribantumab 3,000 mg 1-h IV once weekly at the C1W1, C1W2, C1W3 and C1W4 visits. There were no DLTs observed in the first 6 patients treated with Induction Regimen 2. Upon review and recommendation by the SRC, all subsequently enrolled patients treated under Protocol Version 2.0 initiated treatment with Induction Regimen 2.

With IRB/IEC approval of Protocol Version 3.0, subsequently enrolled patients initiated treatment with the 12-Week Target Induction Regimen.

12-Week Target Induction Regimen: Seribantumab 3,000 mg 1-h IV once weekly for a total of 12 weeks (C1W1, C1W2, C1W3, C1W4, C2W1, C2W2, C2W3, C2W4, C3W1, C3W2, C3W3, and C3W4 visits). Notably, patients enrolled to Induction Regimen 2, who were continuing weekly induction phase dosing at the time of IRB approval for Protocol Version 3.0, were switched to the extended 12-Week Target Induction Regimen.

Q2 Week Dosing:

Prior to IRB/IEC approval of Protocol Version 4.0, all patients who completed induction phase dosing with Induction Regimen 1, Induction Regimen 2 or the 12-week Target Induction Regimen, who continued study-directed treatment, subsequently received seribantumab 3,000 mg 1-h IV once every 2 weeks, initiating approximately 14 days after completion of the final weekly induction dosing. For these patients, dosing continued every 2 weeks until patients met one or more protocol-specific treatment discontinuation criteria.

Protocol Version 2.0 included Q2W dosing for 6 doses (consolidation dosing) followed by Q3W dosing (maintenance dosing) for the remainder of study participation. Q3W dosing was removed from the protocol with the approval of Protocol Version 3.0. No patients were treated with Q3W dosing.

APPENDIX B: MOST/CRESTONE COUNTRY SPECIFIC APPENDIX (AUSTRALIA ONLY)

MoST CRESTONE:
Seribantumab

MoST CRESTONE: Australia Specific Appendix to the International CRESTONE Study

Australia Specific Appendix version 5.0 dated XX September 2022, to the CRESTONE Trial Protocol version 7.0, dated 21 September 2022

IMPORTANT NOTE
This appendix is to be read in conjunction with the current approved version of the CRESTONE Trial Protocol. This document provides additional information about trial structure and conduct specifically in Australia.

Protocol Title	CRESTONE: A Phase 2 Study of Seribantumab in Adult Patients with Neuregulin-1 (NRG1) Fusion Positive Locally Advanced or Metastatic Solid Tumors
Short Title:	MoST CRESTONE
CTC Protocol Number:	CTC 0369
Global Sponsor (CRESTONE):	Elevation Oncology
Australian Sponsor:	University of Sydney
Australian Coordinating Principal Investigator:	Subotheni Thavaneswaran

MoST CRESTONE:
Seribantumab

Australia-specific protocol information for conduct of the CRESTONE study (ELVCAP-001-01)

IMPORTANT NOTE

Unless otherwise specified, the information below is *in addition* to that included in the CRESTONE Trial Protocol. Where information in the appendix conflicts with that in the CRESTONE Trial Protocol, the appendix will take precedence.

"MoST CRESTONE" refers to a subset of up to 16 Australian participants who will receive treatment with seribantumab for NRG1 fusion positive locally advanced or metastatic solid tumours. MoST CRESTONE represents the Australian patients contributing to the global CRESTONE study (ELVCAP-001-01).

MoST CRESTONE will recruit to the pivotal cohort (Cohort 1). With the release of CRESTONE Protocol Version 5.0, exploratory Cohort 3 was closed to enrollment. Under Protocol Version 5.0/Protocol Administrative Letter 8.0, exploratory Cohort 2 was closed to enrollment. Should recruitment to the global CRESTONE study cease for reasons other than futility or safety, it is envisaged that participants will continue to enroll in Australia until the target enrollment of 16 participants is reached.

The following section of this document (Section 3) describes Australian-specific variations to the conduct of the global CRESTONE study (ELVCAP-001-01).

List of Abbreviations for this document

Abbreviation	Definition
HREC	Human research ethics committee
IMP	Investigational medicinal product
MoST	Cancer Molecular Screening and Therapeutics
NHMRC CTC	NHMRC Clinical Trials Centre, University of Sydney
OS	Overall survival
PFS	Progression-free survival
SADR	Serious adverse drug reaction
SSI	Significant safety issue
SUSAR	Suspected unexpected serious adverse reaction
TGA	Therapeutic Goods Administration
TMC	Trial Management Committee
TTP	Time to progression
USM	Urgent safety measure

Study Synopsis

Australian Sponsor	The University of Sydney, NSW 2006, Australia
CTC Protocol Number:	CTC 0369
Estimated Number of Patients	Up to 16 patients will be enrolled in Australia as part of MoST CRESTONE. Patients enrolled in Australia may contribute to Cohort 1, 2 or 3 of the global CRESTONE study. With the release of CRESTONE Protocol Version 5.0, exploratory Cohort 3 was closed. Under Protocol Version 5.0/Protocol Administrative Letter 8.0, exploratory Cohort 2 was closed. Cohort 1: patients with centrally confirmed NRG1 gene fusions who are ERBB/HER2/HER3 treatment-naïve AND harbor NRG1 gene fusions with an EGF-like domain intact. Cohort 1 will include patients that have received ≥ 1 prior standard first-line therapy in the locally advanced or metastatic setting. Cohort 2: Under Protocol Version 5.0/Protocol Administrative Letter 8.0, enrollment to Cohort 2 was closed. Patients with NRG1 fusions with an EGF-like domain intact, who have received ≥ 1 prior standard therapy, in the locally advanced or metastatic setting including prior ERBB/HER2/HER3 directed treatment. Cohort 3: Enrollment to Cohort 3 was closed under Protocol Version 5.0. Patients with NRG1 fusions without an EGF-like domain including but not limited to NRG1-PMEPA1, NRG1-STMN2, PCM1-NRG1 and INTS9-NRG1; patients with NRG1 fusions and other molecular aberrations lacking standard treatment options.
Primary objective *[Note: this section is reproduced verbatim from the CRESTONE Protocol for readability of this appendix]*	To determine the objective response rate by independent radiologic review to single agent seribantumab (anti-HER3 targeted therapy) in patients with centrally confirmed NRG1 gene fusion positive advanced cancer according to RECIST 1.1.
Secondary Objectives	Additional secondary objectives for MoST CRESTONE population include: • The ratio of time to progression (TTP) on MoST CRESTONE (TTP2) to TTP in the period prior to MoST CRESTONE (TTP1) • Progression free survival at 6 months • Overall survival at 12 months
Study Design	Up to 16 participants will be enrolled to this study in Australia as part of MoST CRESTONE. Potential participants may be identified via their participation in molecular screening programs, such as the MoST

	Framework Protocol screening program.
Statistical Considerations and Data Reporting *[Some content in this section is reproduced from the CRESTONE Protocol for readability of this appendix]*	Please refer to Section 10 of the Global CRESTONE protocol for information on statistical methods. MoST CRESTONE will recruit participants in Australia to a maximum of 16 participants. Data collected from these participants will be included in the overall analysis for the global CRESTONE study. Additionally, upon completion of recruitment in Australia, the Australian treatment outcomes will be described in a subsequent and separate sub-group analysis. Categorical variables will be summarized by frequency distributions (number and percentages of patients) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, maximum). 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.

Section 2 Objectives

Aim: To assess the clinical activity of seribantumab in patients with NRG1 fusion positive locally advanced or metastatic solid tumours.

Section 2.1 Primary objective

[This section is reproduced verbatim from the CRESTONE Protocol for readability of this appendix]

To determine the objective response rate by independent radiologic review to single agent seribantumab (anti-HER3 targeted therapy) in patients with centrally confirmed NRG1 gene fusion positive advanced cancer according to RECIST 1.1.

Section 2.2 Secondary objectives

Additional secondary objectives for MoST CRESTONE population include:

- The ratio of time to progression (TTP) on MoST CRESTONE (TTP2) to TTP in the period prior to MoST CRESTONE (TTP1)
- Progression free survival at 6 months
- Overall survival at 12 months

Section 3.1 Study Design

MoST CRESTONE is the subset of patients enrolled to the global multicenter open-label phase II clinical study in Australia. Participants must be eligible for one of the actively enrolling cohorts described in the global CRESTONE protocol (ELVCAP-001-01).

MoST CRESTONE will represent the Australian subset of patients contributing to the global CRESTONE study (ELVCAP-001-01). MoST CRESTONE will recruit to the pivotal cohort (Cohort 1) and the two exploratory cohorts (Cohorts 2 and 3). With the release of CRESTONE Protocol Version 5.0, exploratory Cohort 3 was closed to enrollment. Under

Protocol Version 5.0/Protocol Administrative Letter 8.0, exploratory Cohort 2 was closed to enrollment.
Should recruitment to the global CRESTONE study cease for reasons other than futility or safety, it is envisaged that participants will continue to enroll in Australia until the target enrollment of 16 participants is reached.
The MoST CRESTONE population will be included in the overall analysis of the global CRESTONE study. In addition, the MoST CRESTONE subset of patients will be analysed and published subsequently and separately from the global CRESTONE analysis to describe the Australian treatment experience and outcomes with seribantumab.

Section 3.4 MoST CRESTONE Coordination

Coordination and statistical analysis of the MoST CRESTONE population will be performed by the NHMRC CTC. MoST CRESTONE study results will be a sub-group analysis and published as a sub-group of the global CRESTONE study (ELVCAP-001-01). Data collected from patients participating in Australia will be included in the global CRESTONE analysis and resulting publication.

Section 4 Study Population

No exceptions will be made to these eligibility requirements at the time of registration.
All enquiries about eligibility should be addressed by contacting Elevation Oncology (or their nominated delegate) prior to registration.

Section 9.1 Adverse Events

In Australia the following definitions are used for reporting of safety events;

- A SIGNIFICANT SAFETY ISSUE (SSI) is defined as is a safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. These events may be in addition to the current SAE/SADR/SUSAR reports and generally have a consequence related to patient safety within the current study protocol, which thus requires some type of amendment.
- An URGENT SAFETY MEASURE (USM) is one type of significant safety issue where sponsors or trial investigators act immediately to protect participants from an immediate hazard to their health and safety. USMs are often instigated before the TGA and HREC are notified. In these cases, it is strongly recommended that the sponsor contact the TGA within 24 hours of the measure being taken.

(Examples include:

- a serious adverse event that could be associated with the trial procedures and that requires modification of the conduct of the trial
- a hazard to the patient population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease
- a major safety finding from a newly completed animal study (such as carcinogenicity)
- a temporary halt/termination of a trial for safety reasons
- recommendations of the Safety Review Committee, where relevant for the safety of participants, such as an increase in frequency or severity of an expected adverse reaction

- single case events (e.g. toxic epidermal necrolysis, agranulocytosis, hepatic failure) that lead to an urgent safety measure)

SSIs or USMs do not necessarily meet all criteria to be considered an SAE. For purpose of safety reporting, these events are to be reported in real-time (within 24 hours of awareness) to NHMRC CTC and Elevation Oncology (or their nominated delegate) with a note that this concerns an SSI or USM.

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that is related to the drug or device and is unexpected, i.e. not listed in the investigator brochure or approved Product Information; or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the Participant Information Sheet and Informed Consent Form or elsewhere in the protocol. An event is causally related if there is a reasonable possibility that the drug caused the AE, i.e. there is evidence to suggest a causal relationship between the drug and the event.

Section 9.4 Serious Adverse Event Reporting

The investigator is responsible for reporting all SAEs (including SUSARs), SSIs and USMs occurring during the study to the global Sponsor within 24 hours of investigational site staff becoming aware of the event according to the procedure documented in the Study Manual.

The NHMRC CTC will be responsible for providing reports to the Lead HREC. The NHMRC CTC will provide SUSAR, SSIs and USMs reports and SAE line listings to Investigators for submission to Human Research Ethics Committees (HRECs) as required. The investigator must notify the local site as required.

The NHMRC CTC will submit 'reportable safety events' to the TGA in Australia and to the lead site/coordinating centre in other regions, in time to comply with the requisite specified regulatory time windows (usually 7 days for fatal/life threatening events with an 8 day follow-up report, and 15 days for other events). The lead site/centre will be responsible for reporting to the regulatory authorities and Lead Ethics Committees in other participating countries for which they are responsible.

Section 10 Statistical Methods

A full SAP will also be produced for the MoST CRESTONE analyses. Upon completion of Australian recruitment, the Australian treatment outcome will be described.

Section 10.6 Secondary Efficacy Analysis

For the MoST CRESTONE population, additional secondary endpoints are defined as follows:

Time to progression:

Time to progression is defined as the time interval from the date of seribantumab treatment initiation (Dose 1) to the date of first evidence of disease progression on MoST CRESTONE (TTP2) or death due to cancer.

The study will compare the time to progression on MoST CRESTONE (period 2) with the time to progression on the most recent therapy on which the patient had just experienced progression (period 1). If the ratio of TTP of period 2 over TTP of period 1 (TTP2/TTP1) is greater than or equal to 1.3, then the study therapy will be defined as having benefit for the patient, as durable stable disease is achieved. This efficacy assessment is based on

key elements shared with the WINTHER trial conducted by the WIN consortium (NCT01856296). For patients where time to progression prior to trial therapy (TTP1) cannot be evaluated, TTP2 exceeding 6 months (i.e. stable disease on study maintained for > 6 month) would meet the criteria of benefit.
Determination of disease progression will follow the RECIST v1.1 criteria where comparative baseline scan data is available. If surgical intervention is required on a target lesion, this will constitute progression and be censored at the time of surgery. A clinical evaluation will be required.
Progression free survival (PFS) at 6 months:
PFS at 6 months will also be determined. Progression free survival at 6 months is defined as the proportion of patients on study who are alive and progression free at 6 months from date of seribantumab treatment initiation (Dose 1) on study.
Overall survival (OS) at 12 months:
OS at 12 months is defined as the proportion of patients who are alive at 12 months from date of seribantumab treatment initiation (Dose 1) on study to date of death from any cause (or the date of last known vital status during follow up within 12 months from date of seribantumab treatment initiation (Dose 1)).
Duration of response and clinical benefit rate are defined as per the global CRESTONE protocol.

Section 11.3 Trial Ethics

In Australia, the study will be conducted according to the Note for Guidance on Good Clinical Practice (Integrated Addendum to ICH E6 (R1): Guidelines for Good Clinical Practice ICH E6(R2) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans 2007, the NHMRC Australian Code for the Responsible Conduct of Research (2007, *updated 2015 and as amended from time to time),* according to NHMRC Guidance: “Safety monitoring and reporting in clinical trials involving therapeutic goods-Nov2016”, and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008.
To this end, no patient will be recruited to the study until all the necessary approvals have been obtained and the patient has provided written informed consent. Further, the investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a participant. In this circumstance, the NHMRC CTC, global Sponsor, principal investigator and HREC must be advised immediately.

Section 11.4 Patient Informed Consent

A sample pre-screening consent will not be provided in Australia.
A master participant information sheet and consent form, developed by the sponsor and approved by the lead HREC, will be provided to investigators for approval by their local HRECs and/or governance offices as required prior to use.

For patients who meet criteria to continue with treatment beyond progression, as described in Section 5.4.1 of the main protocol, an addendum Treatment Beyond Progression ICF that is developed by the Sponsor and approved by HREC must be signed

by the participant prior to continuing treatment beyond disease progression.

Section 11.5 Investigational Review Board Approval

In Australia, the term "Investigational Review Board" refers to the human research ethics committee (HREC) and/or local governance body reviewing this study. There may be site-specific governance review and approval required at site, in addition to HREC approval. Approval letters may take the form of an email (including automatically generated emails), and do not require letterhead or formal signature.

Section 11.6 Monitoring

Authorisation by participants for the use of personal identifiable health information will be documented via signature on the main participant information sheet and consent form.

Section 11.7 Confidentiality

The study will be conducted in accordance with applicable Privacy laws and regulations. All data generated in this study will remain confidential. All information will be stored securely at the NHMRC CTC, University of Sydney, and Elevation Oncology and Medpace, and will only be available to people directly involved with the study and who have signed a Confidentiality Agreement. Coded information may be shared with future collaborators.

Section 11.8 Protocol Amendments

Changes and amendments to the protocol can only be made by the Sponsor. Approval of amendments by the Institutional HREC is required prior to their implementation. In some instances, an amendment may require a change to a consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the data collected, if required, will be incorporated in the amendment.

The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial participant(s).

Section 11.9 Records Retention

All study-related documentation at Australian sites will be maintained for 15 years following completion of the study, or until 2 years following the date that the last marketing application for the study drug is approved, or if no marketing application is filed, or such application is not approved, for 2 years after the formal discontinuation of clinical development of the study drug – whichever is later.

Signed consent forms from Australian participants will not be collected by the Sponsor or their representative. They must be filed, as appropriate, at each site.

Section 11.10 Clinical Study Report

A Clinical Study Report which summarises and interprets all the pertinent study data collected for the MoST CRESTONE population (population of patients enrolled in Australia) will be issued, which may form the basis of a manuscript intended for publication.