GI 195

Phase II Study of Carfilzomib for the Treatment of Patients with Advanced Neuroendocrine Cancers

SCRI INNOVATIONS STUDY NUMBER:	GI 195
STUDY DRUG:	Carfilzomib
SPONSOR:	SCRI Development Innovations, LLC (SCRI Innovations) 3322 West End Avenue , Suite 900 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@sarahcannon.com
STUDY CHAIR:	Johanna Bendell, MD Director, GI Oncology Research Associate Director, Drug Development Unit Sarah Cannon Research Institute 3322 West End Avenue, Suite 900 Nashville, TN 37203 jbendell@tnonc.com
DATE FINAL:	16 NOVEMBER 2014
AMENDMENT 1	17 DECEMBER 2014
AMENDMENT 2	25 FEBRUARY 2015

SCRI DEVELOPMENT INNOVATIONS

Clinical Study Statement of Compliance

Phase II Study of Carfilzomib for the Treatment of Patients with Advanced Neuroendocrine Cancers

This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Study Chair and/or Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

SCRI DEVELOPMENT INNOVATIONS

Clinical Study Signature Approval Page

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Johanna Bendell, MD

Study Chair	**Study Chair Signature**	**Date**

Sheetal Khedkar

SCRI Development Innovations, LLC	**SCRI Development Innovations, LLC Representative Signature**	**Date**

SCRI DEVELOPMENT[SM] INNOVATIONS

Clinical Study Principal Investigator Signature Form

Phase II Study of Carfilzomib for the Treatment of Patients with Advanced Neuroendocrine Cancers

SCRI INNOVATIONS STUDY NUMBER:	GI 195
DATE FINAL:	16 NOVEMBER 2014
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By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

_____	_____	_____
Principal Investigator Name (Please Print)	**Principal Investigator Signature**	**Date**

Please retain a copy of this page for your study files and return the original signed and dated form to:

SCRI Development Innovations, LLC
3322 West End Avenue, Suite 900
Attn: GI 195 Study Team
Nashville, TN 37203

GI 195 Summary of Changes

AMENDMENT NUMBER:	1	AMENDMENT DATE:	17 DECEMBER 2014

Section 3.1 Inclusion Criterion #3

Patients currently receiving or previously treated with single agent **somatostatin analogues** (e.g. sandostatin LAR® **or lanreotide**) are eligible. However, this is not a mandatory criterion to be included in the study.

Section 3.2 Exclusion Criterion #2

Patients who have had radiation therapy, hormonal therapy, biologic therapy, or chemotherapy for cancer within 21 days or 5 half-lives of any chemotherapy or biologic/targeted agent, whichever is longer, prior to first treatment day of the study. **(Refer to exclusion criterion #8 for restrictions associated with radiation therapy in patients with brain metastases)**

Section 3.2 Exclusion Criterion #4

~~History or known presence of central nervous system (CNS) metastases.~~

Section 5

"Subject" changed to "Patient"

Section 7.6.1 Follow-up for Patients Who Discontinue Prior to Disease Progression

- Physical examination, including ~~measuring your~~ weight and vital signs (includes blood pressure, heart rate, breathing rate, and oral temperature)
- **CBC, including 3-part differential and platelets.** ~~Blood samples for routine laboratory testing.~~
- ~~Blood samples for~~ CMP ~~testing~~
- ~~You will have~~ CT scan of the chest, a CT scan of the abdomen/ pelvis ~~done~~

Appendix D, Footnote o

Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 3 months (±1 month) from the date of last dose of study drug until disease progression. **PFS will be evaluated for this trial 6 and 12 months after the last patient is enrolled**. No follow up will be done for survival or if the patient starts a subsequent therapy.

Minor typographical and grammatical corrections were done throughout the protocol.

Section 2.3: Exploratory objective

The following objective was deleted.

~~To perform whole exome sequencing analysis in optional tumor biopsy samples.~~

Section 4: Patient registration

Registration fax number changed from (866) 699 0258 to (866) 346 1062

Registration Email address was added: CANN.SCRIInnovationsEnr@scri-innovations.com

Section 5.4.1: Tumor Tissue Samples

Archival tumor samples ~~will~~ may be collected during the study with the purpose of identifying molecular alterations relevant to carfilzomib. ~~For patients who participate in the study, whole exome sequencing analysis in optional tumor biopsy samples will be done. This material should be provided as a tissue block or 10 paraffin-dipped unstained slides. The status of gene mutation and protein expression by IHC will be tested to explore whether these are correlated with the response to treatment.~~

~~We hope to have evaluable biopsy data in approximately 10% of the patients. In order to do this, we plan to collect biopsies in 20% of patients. A pre-treatment biopsy and a repeat biopsy on Day 15(± 1) Cycle 1 will be optional but preferable. The samples will be analyzed in house at Onyx.~~

~~For collection, shipment, handling, etc. of tumor biopsy samples see the Laboratory Manual.~~

Section 7.2: Baseline study assessment

~~Fresh (optional) tumor biopsy sample, if applicable~~

Section 7.3.1: Days 1, 8, and 15 of each cycle

~~Optional biopsy (Cycle 1, Day 15), if applicable~~

Appendix D: Study assessment table

Fresh biopsy collection and footnote "i" has been deleted to reflect the changes.

GI 195 PROTOCOL SYNOPSIS

Title of Study:	Phase II Study of Carfilzomib for the Treatment of Patients with Advanced Neuroendocrine Cancers
SCRI Innovations Study Number:	GI 195
Sponsor:	SCRI Development Innovations, LLC. Nashville, TN
Study Duration:	The total duration of the study is planned to be 24 months. **Phase of Study:** II
Study Centers:	This study will be conducted at multiple sites.
Number of Patients:	Up to 62 patients are planned to be enrolled in this study.
Objectives:	**Primary Objective** The primary objective of this study is to: • To evaluate the overall response rate (ORR) of patients with advanced neuroendocrine tumors treated with carfilzomib. **Secondary Objectives** The secondary objectives of this study are: • To evaluate the disease control rate (DCR) in patients with advanced neuroendocrine cancers treated with carfilzomib. • To evaluate the progression free survival (PFS) of patients with advanced neuroendocrine cancers treated with carfilzomib. • To further evaluate toxicities associated with this regimen. **Exploratory Objective** The exploratory objective of this study is: • To determine the status of gene mutation and protein expression by immunohistochemistry (IHC) on the tumor samples to explore the correlation with the response to treatment will be done.
Study Design:	This Phase II open-label, non-randomized clinical study will be conducted by participating sites in the Sarah Cannon Research Institute network. This study will evaluate the use of carfilzomib for patients with advanced neuroendocrine tumors. Patients will receive treatment by intravenous (IV) infusion over 30 minutes on days 1, 2, 8, 9, 15, and 16 of each cycle. Cycles are 28 days in length. Patients will be evaluated for response to treatment every 3 cycles; responding and/or stable patients will continue treatment, with re-evaluations every 3 cycles, unless tumor progression or intolerable toxicity occurs. Response to therapy will be assigned using RECIST v1.1 criteria.
Study Drugs, Doses, and Modes of Administration:	Carfilzomib will be administered as IV infusion. Patients will receive 20 mg/m^2 on Days 1 and 2 of Cycle 1. Thereafter, patients will receive 56 mg/m^2 on Days 8, 9, 15 and 16. Starting from Cycle 2 patients will receive 56 mg/m^2 on Days 1, 2, 8, 9, 15 and 16.

GI 195 PROTOCOL SYNOPSIS

Inclusion Criteria:	1. Patients with biopsy-proven advanced, unresectable or metastatic, well-to-moderately differentiated (or low-grade) neuroendocrine carcinoma, including typical carcinoid, pancreatic islet cell and other well-to-moderately differentiated neuroendocrine carcinomas. 2. Patients must have at least one unidimensional measurable lesion definable by magnetic resonance imaging (MRI) or computerized tomography (CT) scan. Disease must be measurable per Response Evaluation Criteria in Solid Tumors RECIST version 1.1 criteria (Appendix E). 3. Patients currently receiving or previously treated with single agent somatostatin analogues (e.g. sandostatin LAR® or lanreotide) are eligible. However, this is not a mandatory criterion to be included in the study. 4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of ECOG PS 0 or 1 (Appendix A). 5. Adequate hematologic function defined as: - Absolute neutrophil count (ANC) ≥1500/μL - Hemoglobin (Hgb) ≥9 g/dL - Platelets ≥100,000/μL 6. Adequate liver function defined as: - Alanine aminotransferase (ALT) ≤ 2.5 x ULN **or** <5.0 x ULN in patients with liver metastases - Aspartate aminotransferase (AST) ≤ 2.5 x ULN **or** ≤5.0 x ULN in patients with liver metastases - Total bilirubin ≤1.5 x ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin) 7. Adequate renal function defined as serum creatinine ≤2.0mg/dL **or** calculated creatinine clearance ≥30 mL/min as calculated by Cockcroft and Gault Formula. 8. Women of childbearing potential (WoCBP) must have a negative serum or urine pregnancy test. Serum pregnancy test should be performed ≤7 days or urine pregnancy test will be performed within ≤3 days prior to start of treatment. Another pregnancy test will be performed within 30 days following last dose of study drug. WoCBP or men with partners of childbearing potential must use effective birth control measures during treatment (Appendix C). If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must agree to inform her treating physician immediately. 9. Predicted life expectancy > 12 weeks 10. Age ≥18 years. 11. All patients must be willing to and have the ability to comply with the study and related follow-up procedures. 12. All patients must be able to understand the nature of the study and give written informed consent prior to study entry.

GI 195 PROTOCOL SYNOPSIS

Exclusion Criteria:	1. Patients with poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, globlet cell carcinoid, atypical carcinoid, anaplastic carcinoid, pulmonary neuroendocrine and small cell carcinoma are not eligible 2. Patients who have had radiation therapy, hormonal therapy, biologic therapy, or chemotherapy for cancer within 21 days or 5 half-lives of any chemotherapy or biologic/targeted agent, whichever is longer, prior to first treatment day of the study. (Refer to exclusion criterion #8 for restrictions associated with radiation therapy in patients with brain metastases) . 3. Patients who have received any other investigational agents within the 21 days or 5 half-lives, whichever is longer, prior to first treatment day of the study. 4. Women who are pregnant or lactating. 5. Patients with poorly controlled or clinically significant atherosclerotic vascular disease including the following: - Congestive heart failure (New York Heart Association [NYHA] ≥ Class 3 and 4 heart failure (Appendix B) - Patients with known LVEF<40% - Unstable angina pectoris requiring nitrates within the last 12 months - Acute myocardial infarction, cerebrovascular accident, or transient ischemic attack within the last 12 months - Angioplasty (coronary or vascular) within the last 12 months - Cardiac or vascular stenting in the past 12 months - Ventricular arrhythmia requiring medication within the last 12 months 6. Concurrent severe, intercurrent illness including, but not limited to, ongoing or active infection, or psychiatric illness/social situations that would impair the ability of the patient to receive protocol treatment. 7. Major surgical procedures ≤28 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement. 8. Previously untreated brain metastases. Patients who have received radiation or surgery for brain metastases are eligible if therapy was completed at least 2 weeks prior to study entry and there is no evidence of central nervous system disease progression, mild neurologic symptoms, and no requirement for chronic corticosteroid therapy. 9. Known diagnosis of human immunodeficiency virus, hepatitis B or hepatitis C. 10. Presence of other active cancers or history of treatment for invasive cancer ≤ 5 years. Patients with stage I cancer who have received definitive local treatment at least 3 years previously, and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer. 11. Infection requiring IV antibiotics.
Statistical Methodology:	This is a multicenter, Phase II study of carfilzomib for the treatment of patients with advanced neuroendocrine cancers. Demographic data and baseline disease characteristics will be summarized using appropriate descriptive statistics (e.g., mean, median, standard deviation or percentages and frequency counts). The primary endpoint, ORR, will be determined using RECISTv1.1 criteria. The median and 25% and 75% percentiles for PFS will be summarized with associated 95% CI, and the distribution of PFS will be presented graphically using the Kaplan-Meier approach. Progression-free survival will be evaluated six and 12 months after the last patient is enrolled on the trial.

GI 195 CONTACT INFORMATION

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LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CMP	Comprehensive metabolic profile
CR	Complete response
CT	Computerized tomography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EGFR	Epidermal growth factor receptor
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
GCP	Good Clinical Practice
HGFR	Hepatocyte growth factor receptor
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
MRI	Magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
ORR	Overall response rate
PD	Progressive disease
PDGFR	Platelet-derived growth factor receptors
PHI	Protected health information
PFS	Progression-free survival
PK	Pharmacokinetic
PNET	Pancreatic neuroendocrine tumors
PR	Partial response
PT	Prothrombin
PTT	Partial thromboplastin time
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAR	Suspected adverse reaction

LIST OF ABBREVIATIONS (continued)

SCRI	Sarah Cannon Research Institute
SD	Stable disease
SUSAR	Suspected unexpected serious adverse reaction
TLS	Tumor lysis syndrome
UAE	Unexpected Adverse Event
ULN	Upper limit of normal
WoCBP	Women of childbearing potential

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1. INTRODUCTION

1.1 Background

Neuroendocrine malignancies refer to a diverse group of diseases that are generally rare however, their incidences are rapidly increasing. Among these, pancreatic neuroendocrine tumors (PNETs, islet cell tumor, islet cell carcinoma, or pancreatic carcinoid) account for up to 5% of all pancreatic malignancies. Functional PNET tumors make extra amounts of hormones (e.g. gastrin, insulin, and glucagon) and cause symptoms. Non-functional PNETs do not make extra amounts of hormones, and the symptoms are caused by the tumors as they grow. The majority of the non-functional tumors are malignant.

Gastrointestinal (GI) carcinoids are well-differentiated endocrine neoplasms that consist of a diverse group of tumors arising from cells of the diffuse endocrine system within the GI tract. These tumors are generally slow-growing and can be present throughout the GI tract. All GI carcinoids share common pathologic features that characterize them as well-differentiated neuroendocrine tumors (NETs) (Levy and Sobin. 2007). The World Health Organization (WHO) classification of GI NETs is clinically and prognostically useful for newly diagnosed patients with GI NETs because it accounts for specific biological behavior according to location and tumor differentiation. The specific biological behavior of a particular tumor type varies according to the cell of origin (Capella et al. 1995; Solcia et al. 2000).

1.2 Treatment for pancreatic neuroendocrine tumors (PNET) and gastrointestinal carcinoid tumors

Standard therapy for pancreatic neuroendocrine tumors (PNET) and gastrointestinal carcinoid tumors generally consists of chemotherapy combinations with streptozocin and either flurouracil or adriamycin, which are not very effective (Cheng and Saltz, 1999; McCollum et al. 2004). Neuroendocrine tumors are characterized by high vascularity along with high expression of several pro-angiogenic factors and growth factors and growth receptors (PDGFR), fibroblast growth factor receptor (FGFR), hepatocyte growth factor receptor (HGFR), insulin-like growth factor 1 (IGF-1) receptor, epidermal growth factor receptor (EGFR). One of the major signalling pathways implicated in driving these tumors is the PI3K-AKT-mTOR pathway (Bergers et al. 1999; Phan et al. 2006; Chaudhry et al. 1992; Wulbrand et al. 2000; Nilsson et al. 1992; Papouchado et al. 2005; Vignot et al. 2005). This complex molecular signature led to a randomized phase III trial of sunitinib, a VEGFR tyrosine kinase inhibitor, versus best supportive care in patients with advanced PNET. Results of this trial reported an improvement in response rate (9.3% vs. 0%, p=0.0066) and progression-free survival (PFS, 11.4 vs. 5.5 months, p=0.0001, hazard ratio 0.418 [0.263, 0.662]) with sunitinib in patients with advanced, well-differentiated PNETs (Niccoli et al. 2010; Raymond et al. 2011). Based on this information, sunitinib was approved by the U.S. Food and Drug Administration (FDA) for the treatment of progressive, well-differentiated PNET in patients with unresectable locally advanced or metastatic diseases. The RADIANT-3 study randomized patients to everolimus versus best supportive care (Yao et al. 2011, Afinitor (everolimus) PI 2102). Everolimus

treatment resulted in an improved PFS (11.0 vs. 4.6 months, HR 0.35 [0.27, 0.45] and response rate (5 vs. 2%). Everolimus has also been FDA approved for this patient population.

Clinical trial data for patients with gastrointestinal carcinoid tumors are still emerging. Octreotide, which binds to somatostatin receptors that are ubiquitously expressed in most neuroendocrine tumors, has been shown to control symptoms and delay tumor growth in these patients (Leong et al. 2002; Imtiaz et al. 2000). A recent randomized phase III study with octreotide LAR vs. placebo for patients with metastatic neuroendocrine cancers (PROMID study) showed an improvement in median time to progression (Rinke et al. 2009). In the randomized, double-blind, multicenter trial of everolimus plus octreotide and best supportive care (BSC) vs. placebo plus octreotide and best supportive care for patients with advanced carcinoid tumors (RADIANT-2), a small improvement in progression-free survival was seen for patients treated with everolimus (16.4 versus. 11.3 months, HR 0.77, [0.59, 1.0]) (Pavel et al. 2011). Response rate was 2% for both treatment groups. The use of bevacizumab for these patients is also under evaluation in a large randomized Southwest Oncology Group (SWOG) study whose results are anticipated shortly.

1.3 Carfilzomib

Carfilzomib (KYPROLIS, Onyx Pharmaceuticals, Inc.), an irreversible proteasome inhibitor, is currently approved by the FDA for the treatment of patients with multiple myeloma who have received at least two prior therapies, including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy (Siegel et al. 2012; Herndon et al. 2013; Kyprolis® (carfilzomib) PI 2012). This approval was accelerated based on response rate. In addition, carfilzomib has been studied in other cancer types such as Waldenstrom's macroglobulinemia, non-Hodgkin's lymphoma, mantle cell lymphoma, and a variety of solid tumors. Carfilzomib has a favorable safety profile according to the reported clinical studies.

Carfilzomib is a tetrapeptide epoxyketone-based inhibitor of the chymotrypsin like activity of the 20S proteasome. It is structurally and mechanistically different from the dipeptide boronic acid proteasome inhibitor bortezomib. Carfilzomib also demonstrated less off-target activity compared to bortezomib when measured against a broad panel of proteases including metallo-proteases, aspartyl-proteases, and serine proteases. This selectivity of carfilzomib may contribute to the reduced myelosuppression and neuropathy observed in preclinical studies when compared with bortezomib.

1.3.1 Safety Pharmacology and Toxicology

Based upon *in vitro* and *in vivo* studies, it is anticipated that carfilzomib can induce more intense and sustained proteasome inhibition compared to bortezomib, resulting in potent cytotoxic and pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture (Demo et al. 2007). Treatment of several hematologic tumor cell lines with carfilzomib for as little as 1 hour led to rapid inhibition of proteasome activity followed by an accumulation of polyubiquitinated proteins and induction of apoptosis. Interestingly, carfilzomib also demonstrated cytotoxicity towards tumor cells lines that have acquired resistance to bortezomib (Suzuki et al. 2011; Kuhn et al. 2007). Preclinical studies were done in rats and monkeys where carfilzomib was

administered intravenously (IV) for 5 consecutive days followed by a rest period of 9 days for 2 cycles, showing a proteasome inhibition of more than 80% (Yang et al. 2011).

However, bolus administration of carfilzomib has produced several adverse effects in rats and/or monkeys including cardiovascular, renal, gastrointestinal, renal, hepatic and hematopoietic toxicities, which were reduced with a longer infusion time (Herndon et al. 2013). Carfilzomib also caused embryofetal toxicities in rats and rabbits, but has not shown any signs of teratogenicity. For this reason, pregnancy category D has been assigned for this agent, as the potential benefits in pregnant patient populations outweigh the potential harm to the fetus.

Lastly, carfilzomib has been administered to rats and monkeys for 6 and 9 months, respectively, (once daily dosing on Days 1 and 2 for three consecutive weeks on a 28-day cycle), and was found to be well tolerated at the doses administered, showing more than 80% proteasome inhibition, with no behavioral changes or histological evidence of peripheral neuropathy and no neutropenia. For details refer to the Investigator's Brochure (IB). In contrast, rats and monkeys treated with bortezomib in chronic toxicity studies demonstrated reduced motor activity, convulsions, tremors, and hind-limb paralysis accompanied by histological degeneration in peripheral nerves, as well as significant neutropenia.

1.3.2 Clinical Experience

In the single-arm, multicenter trial of 266 multiple myeloma patients, carfilzomib produced an overall response rate (ORR) of 22.9% (95% confidence interval [CI]:18, 28.5) with a median duration of response of 7.8 months (95% CI: 5.6, 9.2). In this and other studies, carfilzomib was well tolerated and did not seem to cause clinically meaningful peripheral neuropathy. The most commonly reported adverse events (AEs) were fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia. Subsequent studies confirming the benefit of carfilzomib in the treatment of multiple myeloma are ongoing.

In a clinical study, the pharmacokinetics and safety of carfilzomib were evaluated in patients with normal renal function vs. those with mild, moderate, and severe renal impairment, as well as in patients on chronic dialysis, treated with carfilzomib doses of 15 mg/m^2 during cycle 1, 20 mg/m^2 during cycle 2, and 27 mg/m^2 for cycles 3 and beyond (Badros et al. 2013).

Pharmacokinetics data available for the 15 and 20 mg/m^2 dose indicated that the C_{max} and AUC of carfilzomib were similar across all renal function categories following carfilzomib doses of 15 and 20 mg/m^2. Moreover, the overall safety profile was similar in patients in all renal function categories during mean treatment duration of 5.5 months. However, a recent report indicated 6 patients with baseline renal impairment had further renal function deterioration during the study period.

1.4 Rationale for the Study

Proteasomes are multi-catalytic proteinase complexes responsible for degradation of a wide variety of protein substrates, and play many crucial roles in cell proliferation and survival. Intracellular proteins targeted for degradation by the proteasome are first ubiquitinated via the ubiquitin conjugation system. Ubiquitinated proteins are cleaved within the proteasome by one or more of three separate N-terminal threonine protease activities: a chymotrypsin-like activity, a trypsin-like activity, and a caspase-like activity.

In vitro and *in vivo* studies have shown that proteasome inhibitors have activity against a variety of tumor types. Proteasome inhibitors are known to have antiproliferative, proapoptotic, antiangiogenic, and antitumor effects across multiple tumor models (Boccadoro et al. 2005). Preclinical data showed antitumor activity of proteasome inhibitor bortezomib in the PC-12 neuroendocrine cell line (Fenteany and Schreiber. 1996). A subsequent phase II study of bortezomib in 16 patients with PNET or carcinoid resulted in no objective responses (Shah et al. 2004). However, patient numbers were small and there was heterogeneity in tumor type as well as tumor marker status of the patients.

Carfilzomib is an irreversible proteasome inhibitor that showed activity in patients who have failed to respond to bortezomib treatment and it exhibits antiproliferative and proapoptotic activity in solid and hematologic tumor cells *in vitro*. We propose this phase II study to evaluate carfilzomib for patients with advanced neuroendocrine cancers.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objectives of this study are:

- To evaluate the overall response rate (ORR) of patients with advanced neuroendocrine tumors treated with carfilzomib.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the Disease Control Rate (DCR) in patients with advanced neuroendocrine cancers treated with carfilzomib.
- To evaluate the progression free survival (PFS) of patients with advanced neuroendocrine cancers treated with carfilzomib.
- To further evaluate toxicities associated with this regimen.

2.3 Exploratory Objective

The exploratory objective of this study is:

- To determine the status of gene mutation and protein expression by immunohistochemistry (IHC) on the tumor samples to explore the correlation with the response to treatment.

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1 Inclusion Criteria

Patients must meet the following criteria in order to be included in the research study:

1. Patients with biopsy-proven advanced, unresectable or metastatic, well-to-moderately differentiated (or low-grade) neuroendocrine carcinoma, including typical carcinoid,

pancreatic islet cell and other well- to-moderately differentiated neuroendocrine carcinomas.

2. Patients must have at least one unidimensional measurable lesion definable by magnetic resonance imaging (MRI) or computed tomography (CT) scan. Disease must be measurable per Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 criteria (Appendix E).
3. Patients currently receiving or previously treated with single agent somatostatin analogues (e.g. sandostatin LAR® or lanreotide) are eligible. However, this is not a mandatory criterion to be included in the study.
4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of ECOG PS 0 or 1 (Appendix A).
5. Adequate hematologic function defined as:
   - Absolute neutrophil count (ANC) ≥1500/μL
   - Hemoglobin (Hgb) ≥9 g/dL
   - Platelets ≥100,000/μL
6. Adequate liver function defined as:
   - Alanine aminotransferase (ALT) ≤ 2.5 x upper limit of normal (ULN) **or** <5.0 x ULN in patients with liver metastases
   - Aspartate aminotransferase (AST) ≤ 2.5 x ULN **or** ≤5.0 x ULN in patients with liver metastases
   - Total bilirubin ≤1.5 x ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin)
7. Adequate renal function defined as serum creatinine ≤2.0mg/dL **or** calculated creatinine clearance ≥30 mL/min as calculated by Cockcroft and Gault Formula.
8. Women of childbearing potential (WoCBP) must have a negative serum or urine pregnancy test. Serum pregnancy test should be performed ≤7 days or urine pregnancy test should be performed within ≤3 days prior to start of treatment. Another pregnancy test will be performed within 30 days following last dose of study drug. WoCBP or men with partners of childbearing potential must use effective birth control measures during treatment (Appendix C). If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must agree to inform her treating physician immediately.
9. Predicted life expectancy > 12 weeks
10. Age ≥18 years.
11. All patients must be willing to and have the ability to comply with the study and related follow-up procedures.

12. All patients must be able to understand the nature of the study and give written informed consent prior to study entry.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Patients with poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, globlet cell carcinoid, atypical carcinoid, anaplastic carcinoid, pulmonary neuroendocrine and small cell carcinoma are not eligible.
2. Patients who have had radiation therapy, hormonal therapy, biologic therapy, or chemotherapy for cancer within 21 days or 5 half-lives of any chemotherapy or biologic/targeted agent, whichever is longer, prior to first treatment day of the study. (Refer to exclusion criterion #8 for restrictions associated with radiation therapy in patients with brain metastases)
3. Patients who have received any other investigational agents within the 21 days or 5 half-lives, whichever is longer, prior to first treatment day of the study.
4. Women who are pregnant or lactating.
5. Patients with poorly controlled or clinically significant atherosclerotic vascular disease including the following:
   - Congestive heart failure (New York Heart Association [NYHA] ≥ Class 3 and 4 heart failure) (Appendix B)

- Patients with known LVEF<40%
- Unstable angina pectoris requiring nitrates within the last 12 months
- Acute myocardial infarction, cerebrovascular accident, or transient ischemic attack within the last 12 months
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- Cardiac or vascular stenting in the past 12 months
- Ventricular arrhythmia requiring medication within the last 12 months

6. Concurrent severe, intercurrent illness including, but not limited to, ongoing or active infection, or psychiatric illness/social situations that would impair the ability of the patient to receive protocol treatment.
7. Major surgical procedures ≤28 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement.
8. Previously untreated brain metastases. Patients who have received radiation or surgery for brain metastases are eligible if therapy was completed at least 2 weeks prior to study entry and there is no evidence of central nervous system disease progression, mild neurologic symptoms, and no requirement for chronic corticosteroid therapy.
9. Known diagnosis of human immunodeficiency virus, hepatitis B or hepatitis C.
10. Presence of other active cancers or history of treatment for invasive cancer ≤ 5 years. Patients with stage I cancer who have received definitive local treatment at least 3 years previously, and are considered unlikely to recur are eligible. All patients with previously

treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.

11. Infection requiring intravenous (IV) antibiotics.

3.3 Discontinuation from Study Treatment

Patients will be discontinued from study treatment for any of the following reasons:

- Disease progression (patients who are receiving clinical benefit in the opinion of the treating investigator may be allowed to stay on study after consultation with the Medical Monitor.)
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (as indicated in the investigator's discretion)
- Inability of the patient to comply with study requirements
- Patient requests to discontinue treatment
- Patient withdraws consent from the study
- Non-compliance/lost to follow-up
- If a patient becomes pregnant during the study period, treatment will be discontinued to avoid harm to fetus.

After discontinuation from protocol treatment, patients must be followed for AEs for 30 calendar days after their last dose of carfilzomib. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve, because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patients' medical records and as a comment in the electronic Case Report Form (eCRF).

All patients who have Grade 3 or 4 laboratory abnormalities (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the investigator, not likely that these values are to improve. In this case, the investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment in the eCRF.

4. PATIENT REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, treatment alternatives, side-effects, risks, and discomforts. Human protection committee (Institutional Review Board [IRB]) approval of this protocol and consent form is required. Eligible patients who wish to participate in the study will be enrolled into the study.

Registration must occur prior to the initiation of protocol therapy. Patients eligible to participate in the study may be enrolled through the SCRI Innovations Central Enrollment Desk. The enrollment desk may be reached by calling (877) MY-1-SCRI. Registration may be done via fax (866) 346-1062 Monday through Friday, 8:30 a.m. to 4:30 p.m., Central Standard Time, or via email to CANN.SCRIInnovationsEnr@scri-innovations.com. Patient registration will be confirmed via email within 24 hours, or by the next business day.

5. STUDY DESIGN

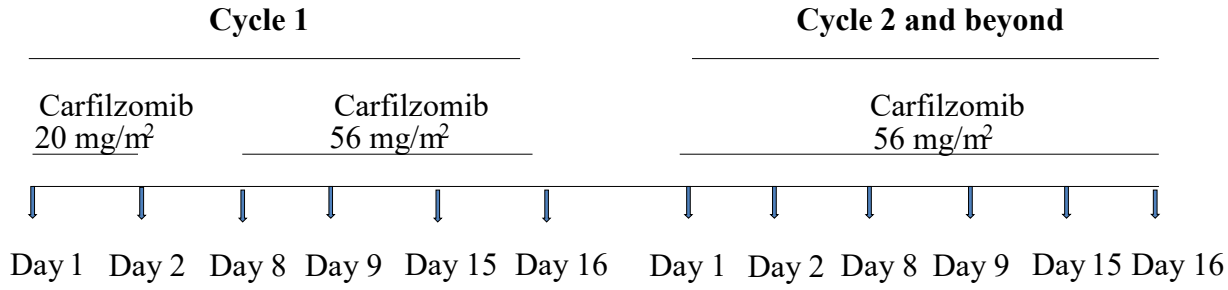
This Phase II open-label, non-randomized clinical study will be conducted by participating sites in the Sarah Cannon Research Institute network. This study will evaluate the use of carfilzomib for patients with advanced neuroendocrine tumors. For the purpose of this study, patients will receive treatment by IV infusion over 30 minutes on days 1, 2, 8, 9, 15, and 16 of each cycle. Cycles are 28 days in length. Patients will receive 20 mg/m^2 on Days 1 and 2 of Cycle 1. Thereafter, patients will receive 56 mg/m^2 on Days 8, 9, 15 and 16. Starting from Cycle 2 patients will receive 56 mg/m^2 on Days 1, 2, 8, 9, 15 and 16. Patients will be evaluated for response to treatment every 3 cycles; responding and/or stable patients will continue treatment, with re-evaluations every 3 cycles, unless tumor progression or intolerable toxicity occurs. Response to therapy will be assigned using RECIST v1.1criteria (see Appendix E).

The doses to be administered on specific treatment days are outlined in the table below. Patients will receive dexamethasone (4 mg for 20 mg/m^2 and 8 mg for 56 mg/m^2) prior to receiving all carfilzomib doses in Cycle 1 and as needed throughout the study to reduce the severity of infusion reactions associated with carfilzomib. The primary endpoints for this study are ORR and PFS.

The planned enrollment for this study is 62 patients.

The study schema is presented in Figure 1.

Figure 1 Study Schema



5.1 Treatment Plan

5.1.1 Carfilzomib

Patients receiving carfilzomib treatment must be hydrated in Cycle 1, and as needed from Cycle 2 onwards, and pre-treated with dexamethasone as indicated below.

Pre-treatment Hydration and Fluid Monitoring

Intravenous (IV) hydration will be given immediately prior to each dose of carfilzomib during Cycle 1; 250 to 500 mL normal saline or other appropriate IV fluid should be given to reduce the risk of renal toxicity and of tumor lysis syndrome (TLS). An additional 250 mL to 500 mL of IV fluids will be given as needed following carfilzomib administration. If lactate dehydrogenase (LDH) or uric acid is elevated (and/or in patients considered still at risk for TLS) at Cycle 2 Day 1, then the recommended IV hydration should be given additionally before each dose in Cycle 2. The goal of the hydration program is to maintain robust urine output (e.g., ≥ 2 L/day). Patients should be monitored periodically during this period for evidence of fluid overload. After Cycle 2, patients will be hydrated at the Investigator's discretion.

If the patient has a dedicated line for carfilzomib administration, the line must be flushed with a minimum of 20 mL of normal saline prior to and after drug administration.

Pre-treatment Dexamethasone

Dexamethasone (4 mg for the 20 mg/m^2 carfilzomib dose and 8 mg for the 56 mg/m^2 carfilzomib dose) PO/IV will be administered prior to all carfilzomib doses during the first cycle and as needed in Cycle 2 and beyond. If treatment-related fever, rigors, chills, and/or dyspnea are observed post any dose of carfilzomib after dexamethasone has been discontinued, dexamethasone (8 mg PO/IV) should be re-started and administered prior to subsequent doses.

TREATMENT SCHEDULE

Carfilzomib 20 mg/m^2 IV will be administered over 30 minutes (± 5 minutes) on Days 1 and 2 of Cycle 1, followed by escalation to 56 mg/m^2 IV over 30 minutes (± 5 minutes) on Days 8, 9, 15, and 16 of Cycle 1. For patients who have adequately tolerated dosing during Cycle 1, carfilzomib 56 mg/m^2 IV will be administered over 30 minutes (± 5 minutes) on Days 1, 2, 8, 9, 15, and 16 of Cycle 2 and beyond. Patients may continue study treatment until intolerable

toxicity, confirmed progressive disease (PD), withdrawal of consent, death, or study closure, whichever occurs earliest. The treatment schedule is provided in the table below.

Table 1 Overall Treatment Plan

DRUG	DOSE	CYCLE	FREQUENCY	Route of Administration
Carfilzomib[a, c]	20 mg/m^2	Cycle 1 only	Days 1, 2	IV over 30 minutes
Carfilzomib[a]	56 mg/m^2	Cycle 1 only	Days 8, 9, 15, 16	IV over 30 minutes
Carfilzomib[b, c]	56 mg/m^2	Cycle 2 and beyond	Days 1, 2, 8, 9, 15, 16	IV over 30 minutes

[a] Carfilzomib 20 mg/m^2 IV will be infused over 30 minutes (± 5 minutes) on Days 1 and 2 of Cycle 1, followed by escalation to 56 mg/m^2 infused over 30 minutes (± 5 minutes) on Days 8, 9, 15, and 16 of Cycle 1.
[b] Carfilzomib 56 mg/m^2 IV will be infused over 30 minutes (± 5 minutes) on Days 1, 2, 8, 9, 15, and 16 of Cycle 2 and beyond.
[c] Study drug will be taken within ± 2 days of the scheduled study day for Day 1 of each Cycle.

Carfilzomib will be administered within ± 2 days of the scheduled study day for Day 1 of each Cycle. Every effort should be made to maintain the dosing schedule as outlined above, and if this is not possible due to extenuating circumstances then priority should be given to maintain consecutive dosing days. If a mid-cycle dose is missed, that dose should be administered no more than 2 days after the scheduled dosing day. Anticipated treatment changes outside of the 2-day window must be discussed with the Medical Monitor or designee.

5.2 Treatment Duration

Patients will be evaluated for toxicity at the start of each cycle. Every 3 cycles, restaging will occur with imaging, laboratory chemistries, and tumor markers as defined in Appendix D. Patients will continue on treatment until progression as defined in Appendix E or intolerance to side effects.

5.3 Concomitant Medications

Carfilzomib is primarily metabolized via peptidase and epoxide hydrolase activities, therefore the pharmacokinetics (PK) profile of carfilzomib should not be affected by concomitant administration of cytochrome P450 (CYP) inhibitors and inducers. Carfilzomib is not expected to influence exposure of other drugs. However, patients will be instructed not to take any additional medications during the course of the study without prior consultation with the research team. At each visit, the patient will be asked about any new medications he is taking or has taken after the start of the study drug.

5.3.1 Permitted Concomitant Medications

Premedication with anti-emetics should be given according to institutional practice.

Medications may be administered for maintenance of existing conditions prior to study enrollment, or for a new condition that develops while on study, including but not limited to the following:

- Allopurinol (or other approved uric acid-lowering agent) in patients at high risk for TLS due to high tumor burden may be prescribed at the investigator's discretion.
- Prophylactic antiviral therapy (e.g., valacyclovir) per institutional standard practice is strongly recommended for patients at increased risk of herpes zoster.
- Patients may receive antiemetics and antidiarrheal agents as necessary.
- Myeloid growth factors (e.g., granulocyte-colony stimulating factor [G-CSF]) may be used if neutropenia occurs in accordance with American Society of Clinical Oncology (ASCO) Guidelines (Smith et al. 2006), but should not be given prophylactically.
- Patients may receive RBC transfusions, erythropoietic stimulating agents, or platelet transfusions at any time.
- Palliative radiation for pain management is permitted with the written approval of the Study Chair. The radiation field cannot encompass a target lesion.

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the investigator with the exception of those listed in Section 5.3.2.

5.3.2 Prohibited Concomitant Medications

The following treatments are prohibited while in this study:

- No other investigational therapy should be given to patients. No anticancer agents other than the study medications should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the study.
- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

5.4 Correlative Studies

5.4.1 Tumor Tissue Samples

Archival tumor samples may be collected during the study with the purpose of identifying molecular alterations relevant to carfilzomib.

6. DOSE MODIFICATIONS

If toxicity occurs, the toxicity will be graded utilizing the NCI CTCAE v4.03 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE), and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity.

Doses of carfilzomib will be modified based on hematologic and non-hematologic toxicity. If dose reductions are necessary, they will be permanent for the remainder of the treatment. Carfilzomib may be adjusted according to the dose modification tables that follow. If the patient is receiving the lowest allowable dose and experiences a toxicity requiring a dose reduction, the offending study drug should be discontinued. Any patient requiring a toxicity-related dose delay of more than 21 days from the intended day of the next scheduled dose must be discontinued from the study.

If patients experience any dose-related toxicity at 20 mg/m^2, they must be discontinued from the study.

A maximum of two dose reductions are allowed in this study. If more than two dose reductions are necessary for a patient, the patient will be discontinued from study treatment.

The dose level reductions to be used in this study are presented in Table 2.

Table 2 Dose Level Modifications

Dose Level	Carfilzomib
Starting Dose	56 mg/m^2
Dose Level -1	45 mg/m^2
Dose Level -2	36 mg/m^2

6.1 Dose Modifications Due to Hematologic Toxicity

If hematologic toxicity occurs, hold all study drugs and re-evaluate in 1 week. Absolute neutrophil count (ANC) and platelets should be monitored weekly until recovery. If ANC and/or platelets do not recover within 3 weeks, the patient will be discontinued from the study.

Dose modifications on Day 1 of each cycle will be based on blood counts determined on the day of scheduled treatment. Nadir blood counts will not be used to determine dose modifications. Dose reductions for hematological toxicities are show in Table 3.

Table 3 Carfilzomib Dose Modifications for Hematologic Toxicities

AE Term and Description	Dose Modification
THROMBOCYTOPENIA	
Grade 3 (25 - <50 x 10^9/L)	1. Interrupt study treatment until toxicity reduced to ≤ Grade 2[a]. 2. If improves in ≤ 7 days, maintain same dose, if > 7 days reduce dose 1 level.
Grade 4 (<25 x 10^9/L)	1. Interrupt study treatment until toxicity reduced to ≤ Grade 2[a]. 2. Restart treatment with a 1 level dose-reduction.
Recurrent Grade 3/4 Event After *Initial Dose Reduction*	1. Interrupt study treatment until toxicity reduced to ≤ Grade 2[a]. 2. Restart treatment with a second 1 level dose-reduction.
Recurrent Grade 3/4 Event After 2 Dose Reductions	***Discontinue***
NEUTROPENIA	
Grade 3 (0.5 x 10^9/L ≤ ANC <1.0 x 10^9/L)	1. Interrupt study treatment until toxicity reduced to ≤ Grade 2[a]. 2. If improves in ≤ 7 days, maintain same dose, if >7 days reduce dose 1 level.
Grade 4 (ANC <0.5 x 10^9/L)	1. Interrupt study treatment until toxicity reduced to ≤ Grade 2[a]. 2. Restart treatment with a 1 level dose-reduction.
Recurrent Grade 3/4 Event After *Initial Dose Reduction*	1. Interrupt study treatment until toxicity reduced to ≤ Grade 2[a]. 2. Restart treatment with a 1 level dose-reduction.
Recurrent Grade 3/4 Event After 2 Dose Reductions	Interrupt until toxicity ≤ Grade [2a] and restart treatment with a 1 level dose-reduction if possible, or discontinue.

a Hold carfilzomib treatment; do at least weekly CBC with differential until toxicity resolves (ANC recovery ≥1.0 x 10^9/L and platelets ≥75 x 10^9/L).

b Re-treatment criteria = ANC recovery ≥1.0 x 10^9/L and platelets ≥75 x 10^9/L.

c Patients who require a treatment delay of more than 3 weeks due to treatment-related toxicity will be discontinued from study treatment, unless the treating physician and the Study Chair agree that continued treatment at lower doses is in the best interest of the patient.

Table 3 Carfilzomib Dose Modifications for Hematologic Toxicities (continued)

AE Term and Description	Dose Modification
FEBRILE NEUTROPENIA	
Grade 3 ANC <1.0 x 10^9/L, fever ≥38.5°C	1. Interrupt study treatment until ANC recovery to ≤ Grade 2[a] (ANC ≥ 1.0 x 10^9/L) and resolution of fever <38.5°C. 2. Restart treatment with a 1 level dose-reduction.
Grade 4 ANC <1.0 x 10^9/L, fever ≥38.5°C and life-threatening consequences	1. Interrupt study treatment until ANC recovery to ≤ Grade 2[a] (ANC ≥ 1.0 x 10^9/L) and resolution of fever <38.5°C and any complications. 2. Restart treatment with a 1 level dose-reduction.

a Hold carfilzomib treatment; do at least weekly CBC with differential until toxicity resolves (ANC recovery ≥1.0 x 10^9/L and platelets ≥75 x 10^9/L).
b Re-treatment criteria = ANC recovery ≥1.0 x 10^9/L and platelets ≥75 x 10^9/L.
c Patients who require a treatment delay of more than 3 weeks due to treatment-related toxicity will be discontinued from study treatment, unless the treating physician and the Study Chair agree that continued treatment at lower doses is in the best interest of the patient..

6.2 Dose Modifications for Non-Hematologic Toxicity

The dose reduction guidelines for non-hematologic toxicities are shown in Table 4.

Table 4 Carfilzomib Dose Reductions for Grade 3 or 4 Non-Hematologic Toxicities

Event	Action to be Taken
Allergic reaction/hypersensitivity Grade 2 – 3 Grade 4	Hold until ≤ Grade 1, reinstitute at full dose. Discontinue
Tumor lysis syndrome (≥ 3 of following: ≥ 50% increase in creatinine, uric acid, or phosphate; ≥ 30% increase in potassium; ≥ 20% decrease in calcium; or ≥ 2-fold increase in LDH	Hold carfilzomib until all abnormalities in serum chemistries have resolved. Reinstitute at full doses.
Infection Grade 3 or 4	Hold carfilzomib (no more than 3 weeks) until systemic treatment for infection complete. If no neutropenia, restart at full dose. If neutropenic, follow neutropenic instructions (Table 3).
Herpes zoster or simplex of any grade	Hold carfilzomib until lesions are dry. Reinstitute at full dose.
Neuropathy Grade 2 treatment emergent neuropathy with pain or Grade 3 neuropathy Grade 4 neuropathy	Continue to dose. If neuropathy persists for more than two weeks hold carfilzomib until resolved to ≤ Grade 2 without pain. Then restart at 1 dose decrement. Discontinue carfilzomib
Renal Dysfunction	Please refer to Table 5.
Congestive heart failure	Any patient with symptomatic congestive heart failure, whether or not drug related, must have the dose held until resolution or return to baseline, after which treatment may continue at a reduced dose, or the patient may be withdrawn from the study. If no resolution after 2 weeks, the patient will be withdrawn from the study.
Other non-hematologic toxicity assessed as carfilzomib-related ≥ Grade 3	Hold dose until toxicity resolves to ≤ Grade 1 or baseline. Restart at 1 dose decrement.

a Carfilzomib should be held until toxicity resolves to ≤ Grade 1. Patients who develop irreversible Grade 3/4 non-hematologic toxicity, or toxicity that does not resolve to ≤ Grade 1 within 3 weeks, should be removed from the study.
b No more than 2 dose reductions of carfilzomib are allowed.

Table 5 Recommended Action for Renal Dysfunction

Renal Dysfunction	Recommended Action
≥ 0 and < 25% decrease in CrCl over baseline	Based on investigator judgment; no dose modification may be necessary.
≥ 25% and < 50% decrease in CrCl over baseline	Hold carfilzomib dose until CrCl is stable. If attributable to carfilzomib, resume carfilzomib at one dose decrement. If not attributable to carfilzomib, restart at dose used prior to the event.
≥ 50% decrease in CrCl over baseline or CrCl < 15 mL/minute (NCI-CTC Grade 4)	Hold carfilzomib dose until CrCl improves to < 25% decrease over baseline and CrCl returns to ≥ 15 mL/ minute (if CrCl dropped to < 15 ml/min). If attributable to carfilzomib, resume carfilzomib at one dose decrement. If not attributable to carfilzomib, restart at dose used prior to the event. If dialysis is required, may resume at a maximal dose of 20 mg/m2 and administer the carfilzomib after dialysis.

7. STUDY ASSESSMENTS AND EVALUATIONS

7.1 Overview

All patients should visit the study center on the days specified within this protocol. The complete Schedule of Assessments for this study is shown in Appendix D. The baseline physical examination, medical history, ECOG PS, 12-lead electrocardiogram (ECG), complete blood counts (CBC), differential and platelets, complete metabolic profile (CMP), prothrombin/partial thromboplastin time/international normalization ratio (PT/PTT/INR), and serum pregnancy test should be done ≤7 days prior to initiation of treatment. If urine pregnancy test is being done, it must be performed within 72 hours of Cycle 1 Day 1. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated on Cycle 1 Day 1. CT scans and LVEF assessment should be performed ≤28 days prior to initiation of treatment, as should tumor markers, if appropriate.

7.2 Baseline Study Assessments

The following information will be collected and procedures will be performed for each patient at screening:

- Written informed consent prior to any other study-related procedures

- Medical history (including clinical tumor assessment as appropriate)
- Physical examination, measurements of height (first visit), weight,
- Vital signs (resting heart rate, blood pressure [BP], respiratory rate, and oral temperature)
- ECOG performance status (see Appendix A)
- 12-lead electrocardiogram (ECG)
- Echocardiogram (ECHO) with calculated left ventricular ejection fraction (LVEF) (repeat if/when clinically indicated). Multigated acquisition (MUGA) scan is acceptable if ECHO is not available.
- Concomitant medication review
- CBC including hemoglobin, hematocrit, WBC with 3-part differential and platelets
- CMP to include: glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, carbon dioxide (CO_2), ALT, AST, alkaline phosphatase (ALP), total bilirubin, total protein, and albumin.
- PT/PTT/INR
- Fasting serum chromogranin A (overnight fasting required)
- Serum (within 7 days) or urine (within 72 hours) pregnancy test must be done before Cycle 1 Day 1
- CT scans of the chest, abdomen and pelvis ≤28 days prior to initiation of study treatment; CT scan of abdomen and pelvis is preferred, but CT scan of abdomen is acceptable.
- Archival tumor tissue or 10 unstained slides will be obtained if available

7.3 Study Treatment Assessments

7.3.1 Days 1, 8, and 15 of each cycle

- Physical examination including measurement of weight, (Day 1 only)
- Vital signs
- ECOG performance status
- Adverse event (AE) assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets (may be done up to 72 hours prior to treatment)
- CMP (may be done up to 72 hours prior to treatment)
- Fasting serum chromogranin A (Day 1 only)
- 24-hour urine for 5-HIAA (Day 1 only)

7.3.2 Days 2, 9, and 16 of each cycle

- Vital signs
- AE assessment
- Concomitant medication review

7.4 Response Assessment Every 3 Cycles

Patients will be evaluated for response to treatment after every 3 cycles of treatment. The following assessments will be performed:

- CT scans of chest, abdomen and pelvis (if abnormal at baseline)
- 24 hour urine for 5-HIAA

Patients with progressive disease or unacceptable toxicity should be discontinued from the study; patients with stable disease or response to therapy will continue treatment.

7.5 End of Study Treatment

The follow-up evaluations required after treatment ends due to completion of the planned study treatment period, disease progression, or once the patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the study physician are specified in Appendix D.

After withdrawal from or completion of protocol treatment, patients must be followed up for AEs for 30 calendar days after the last dose of study drug. The following assessments will be performed:

- Physical examination including measurement of weight
- Medical history
- Vital signs
- ECOG performance status
- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets
- CMP
- Serum or urine pregnancy test
- CT scans of chest, abdomen and pelvis, if no disease progression or not done within prior 6 weeks.

7.6 Follow-up

7.6.1 Follow-up for Patients Who Discontinue Prior to Disease Progression

Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 3 months (±1 month) from the date of last dose of study drug until disease progression. Tests to be performed are listed in Appendix D. Patients will not be followed up for survival if they start any subsequent therapy.

The following tests will be done during follow up visits:

- Medical history will be updated
- Physical examination, including weight and vital signs (includes blood pressure, heart rate, breathing rate, and oral temperature)
- CBC, including 3-part differential and platelets
- CMP
- 24-hour urine collection for 5-HIAA testing
- CT scan of the chest, a CT scan of the abdomen/pelvis .

8. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

8.1 Carfilzomib

Carfilzomib is a synthetic small molecule peptide bearing the chemical name (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide.

Investigational Product	Dosage Form and Strength	Manufacturer
Carfilzomib	60 mg	Onyx Therapeutics, Inc.

8.1.1 Labeling, Packaging, and Supply

Carfilzomib for Injection is supplied as a lyophilized parenteral product in single-use vials packaged in multi-vial cartons. Institutional pharmacies will be supplied with open stock vials with full-disclosure labels.

The immediate packaging will contain a statement to conform with U.S. Food and Drug Administration (FDA) Investigational New Drug (IND) requirements as follows: Caution: New Drug - Limited by Federal (or United States) law to investigational use.

All study drugs must be kept in a secure place under appropriate storage conditions. Storage conditions for carfilzomib are included on the investigational product label.

SCRI Innovations must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

8.1.2 Preparation and Administration of Carfilzomib

For the purpose of this study, carfilzomib will be administered as an IV infusion over 30 minutes.

Preparation and administration instructions will be provided in the pharmacy instruction.

8.1.3 Infusion reaction

Infusion reactions associated with IV administration of carfilzomib were characterized by a spectrum of systemic symptoms including fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately or up to 24 hours after administration. Administration of dexamethasone prior to carfilzomib dosing reduce the incidence and severity of reactions. Inform patients of symptoms and ask them to contact physician if symptoms of an infusion reaction occur. Infusion reactions should be treated as per institutional protocol.

Infusion reactions (e.g., rash, urticaria, erythema, pruritus, bronchospasm, and hypotension) can occur with the agent used in this study. To identify the grade of a reaction, refer to the list below adapted from the General Disorders and Administration Site Conditions section of the NCI CTCAE v 4.03:

- Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated.
- Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids indicated for ≤24 hours).
- Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic mediation and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae. Note: any infusion that is interrupted and not resumed within the visit will be considered a Grade 3 reaction.
- Grade 4: Life-threatening consequences; urgent intervention indicated.

Minor symptoms such as flushing, skin reactions, dyspnoea, lower back pain, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnoea requiring bronchodilators, angioedema or generalized urticaria may require immediate treatment discontinuation and aggressive symptomatic therapy. Patients who experience a severe reaction should not be re-challenged.

Patients who experience an allergic/infusion reaction may be pre-medicated for subsequent cycles per local guidelines and clinical practice.

8.1.4 Precautions and Risks Associated with Carfilzomib

Precautions and risks are located in the IB.

8.2 Accountability for All Study drugs

The Principal Investigator (or designee) is responsible for accountability of all used and unused study drug supplies at the site.

All study drug inventories must be made available for inspection by SCRI Innovations or its representatives and regulatory agency inspectors upon request.

At the end of the study, all SCRI Innovations Drug Accountability Record Form(s) will be completed by the site and sent to the SCRI Innovations Regulatory Department. Study drug supplies must not be destroyed unless prior approval has been granted by SCRI Innovations. Please contact SCRI Innovations regarding disposal of any study drug.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (see Appendix E). Lesions are either measurable or non-measurable according to the criteria. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

This is a multicenter, Phase II study of carfilzomib for the treatment of patients with advanced neuroendocrine cancers.

Demographic data and baseline disease characteristics will be summarized using appropriate descriptive statistics (e.g., mean, median, standard deviation or percentages and frequency counts).

The primary endpoint, ORR, will be determined using RECIST v1.1 criteria. The median and 25% and 75% percentiles for PFS will be summarized with associated 95% CI, and the distribution of PFS will be presented graphically using the Kaplan-Meier approach. Progression-free survival will be evaluated six and 12 months after the last patient is enrolled on the trial.

10.2 Sample Size Considerations

This study will enroll up to 62 patients. Simon's optimal two-stage design (Simon, 1989) will be used for go/no go decision making. The null hypothesis that the true response rate is 0.05 will be

tested against a one-sided alternative. In the first stage, 23 patients will be accrued. If there is 1 or no response in these 23 patients, the study will be stopped. Otherwise, 33 additional patients will be accrued for a total of 56. The null hypothesis will be rejected if at least 6 responses are observed in 56 patients. This design yields a type I error rate of 0.05 and power of 80% when the true response rate is 0.15. The sample size will be increased by 10% to an accrual of 62 patients, to account for potential non-evaluability.

10.3 Analysis Population

The following analysis populations will be used:

- The Full Analysis Set (FAS) will consist of all enrolled patients who receive at least one full or partial dose of study group and who have measurable disease at baseline.
- The Evaluable Population will consist of the subset of the FAS who receive at least 2 full cycles of study drug and who no major protocol violations or deviations.
- The Safety Population is defined as all patients who have received at least one full or partial dose of study treatment and for whom post baseline safety assessments are available.

10.4 Data Analysis

Descriptive statistics, including mean, median, standard deviations and ranges for all continuous measures will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. For time to event outcomes, the median and 25% and 75% percentiles will be summarized with associated 95% confidence intervals. All statistical analyses will be performed using SAS 9.1 or higher. Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized. Data to be tabulated will include demographic features such as age, sex and race, as well as disease-specific characteristics.

The number and percentages of patients enrolled, treated, completing the treatment/study and withdrawn from treatment/study for any reasons will be summarized.

10.4.1 Efficacy Analysis

Efficacy analyses will be reported for FAS population. Additionally, the ORR, Clinical Benefit Rate (CBR), and PFS will be summarized for the Evaluable Population. The following outcomes will be used to evaluate the clinical benefit of the study treatment:

- Overall Response Rate (ORR) is defined as the proportion of patients with confirmed complete response (CR) or partial response (PR (i.e. 2 CRs or PRs at least 4 weeks apart) according to RECIST v1.1 criteria.

- Clinical Benefit Rate (CBR) is defined as the proportion of patients with CR, PR or stable disease (SD) (≥ 6 cycles) according to RECIST v1.1 criteria.

- For ORR and CBR, patients without a post-baseline tumor assessment will be classed as not evaluable (NE) and considered as non-responders.

- Progression-free Survival (PFS) is defined as the time from the first day of study drug administration (Day 1) to disease progression as defined by RECIST v1.1 criteria, or death on study. Patients who are alive and free from disease progression will be censored at the date of last tumor assessment.

For ORR and CBR, the estimates and the associated 95% CI based on the Clopper-Pearson method will be calculated. For PFS, Kaplan-Meier curves will be generated and the median time to event and the associated 95% CI be provided.

Safety Analysis

Safety will be assessed through the analysis of the reported incidence of treatment-emergent AEs. Treatment-emergent AEs are those with an onset on or after the initiation of therapy, and will be graded according to NCI CTCAE v4.03. A copy of CTCAE scoring system may be downloaded from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE.

The AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA), and summarized using system organ class and preferred term for all patients in the Safety Population. In addition, summaries of serious adverse events (SAEs), AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE grade, and AEs related to study treatment will also be presented.

Other safety endpoints including changes in laboratory results, vital signs and ECG findings will be summarized for the safety population. Summaries of laboratory abnormalities based on maximum CTCAE grading will also be produced.

10.5 Analysis Time Points

10.5.1 Final Analysis

The final analysis of the study will occur when all patients progress or, for any patients with a sustained response or stable disease, a minimum of 3 treatment cycles have been completed.

10.5.2 Planned Interim Analysis

No interim analyses are planned. Interim results may be presented at congress prior to final study report, if applicable. The design follows that of Simon et al. 1989. If < 2 of the initial 23 patients enrolled in the study fail to achieve a response, the study will be stopped and the remaining 33 additional patients will not be enrolled. Patients will be evaluated for response to treatment every 3 cycles. Patients will be removed from treatment at the time of disease progression. Patients demonstrating an extended period of stable disease will be considered non-responders after 12 cycles of treatment.

10.5.3 Efficacy Review

Not applicable.

11. SAFETY REPORTING AND ANALYSES

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs, measurement of protocol-specified hematology, clinical chemistry, and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

The Principal Investigator is responsible for recognizing and reporting AEs to the SCRI Innovations Safety Department (SCRI Innovations SD) (see Section 11.1.5). It is SCRI Innovations SD's responsibility to report relevant SAEs to the applicable local or national regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of that IRB.

The Principal Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

11.1 Definitions

11.1.1 Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also known as adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgement about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, dose or including overdose.

11.1.2 Serious Adverse Event

An AE or a suspected adverse reaction (SAR) is considered "serious" if it results in any of the following outcomes:

- **Death**
- **A life-threatening AE**, defined as any adverse experience that places the subject, in the view of the Investigator, at immediate risk of death at the time of occurrence; i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- **Inpatient hospitalization of at least 24-hours or prolongation of existing hospitalization**
- **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
- **A congenital anomaly/birth defect**

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias

or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

It is important to distinguish between "serious" and "severe" AE, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. Seriousness serves as the guide for defining regulatory reporting obligations. "Serious" is a regulatory definition and is based on patient/event outcome or action usually associated with events that pose a threat to a patient's life or vital functions. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the eCRF and SAEs on the SAE Report Form.

11.1.3 Adverse Reaction

An adverse reaction (AR) means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is a reason to conclude that the drug caused the event.

11.1.4 Suspected Adverse Reaction

Suspected adverse reaction (SAR) means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the adverse event. An SAR implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

11.1.5 Recording and Reporting of Adverse Events

Recording of Adverse Events

All AEs of any patient during the course of the research study will be recorded in the eCRF, and the investigator will give his or her opinion as to the relationship of the AE to the study drug treatment (i.e., whether the event is related or unrelated to study drug administration).

All AEs should be documented. A description of the event, including its date of onset and resolution, whether it constitutes a serious adverse event (SAE) or not, any action taken (e.g., changes to study treatment), and outcome, should be provided, along with the investigator's assessment of causality (i.e., the relationship to the study treatment[s]). For an AE to be a suspected treatment-related event there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE v4.03, and changes will be documented.

If the AE is serious, it should be reported immediately to SCRI Innovations SD. Other untoward events occurring in the framework of a clinical study are to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms; abnormal test findings; changes in physical examination; hypersensitivity; and other measurements that occur will be reported as an AE, and collected on the relevant eCRF screen.

Test findings will be reported as an AE if: the test result requires an adjustment in the study drug(s) or discontinuation of treatment, and/ or test findings require additional testing or surgical intervention, a test result or finding is associated with accompanying symptoms, or a test result is considered to be an AE by the investigator.

Reporting Period for Adverse Events

All AEs regardless of seriousness or relationship to carfilzomib treatment (called study treatment), spanning from the start of study treatment, until 30 calendar days after discontinuation or completion of study treatment as defined by the clinical study for that patient, are to be recorded on the corresponding screen(s) included in the eCRF.

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the eCRF screen.

After 30 days of completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

11.1.6 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

> **YES:** There is a plausible temporal relationship between the onset of the AE and administration of the study medication, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies, and/or the AE follows a known pattern of response to the study drug, and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
>
> **NO:** Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or the AE has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed 2 days after first dose of study drug).

11.2 Serious Adverse Event Reporting by Investigators

Adverse events classified by the treating investigator as serious require expeditious handling and reporting to SCRI Innovations SD in order to comply with regulatory requirements. Determination of life-threatening or serious is based on the opinion of either the Sponsor or the Investigator.

Serious AEs may occur at any time from the start of study treatment through the 30 days after the last dose of study drug. **The SCRI Innovations SD must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.**

To report a SAE, the SAE Report Form should be completed with the necessary information.

The SAE report should be sent to SCRI Innovations SD via fax or e-mail using the using the following contact information (during both business and non-business hours):

SCRI Innovations Safety Department

Safety Dept. Fax #: 1-866-807-4325

Safety Dept. Email: CANN.SAE@SCRI-Innovations.com

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to SCRI Innovations SD as soon as it is available; these reports should be submitted using the SCRI Innovations SAE Report Form. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the study reference manual.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB.

Expedited Reporting by Investigator to Onyx

Expedited reporting will be completed by the Sponsor Safety Department of SCRI Innovations Safety Department. Expedited reports will not be sent to Onyx by the Site investigator. SAE reports are submitted by the participating site investigator with 24 hours of awareness to the SCRI Innovations Safety Department. The Expedited Reporting responsibilities belong to SCRI Innovations Safety Department.

CAR-XXX and the institutional protocol number should be included on all reports to Onyx.

Onyx Drug Safety and Pharmacovigilance Contact Information:

Onyx Fax: (800) 783-7954

Email: Adverse.Events@onyx.com

11.3 Recording of Adverse Events and Serious Adverse Events

11.3.1 Diagnosis vs. Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Principal Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF screen). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as an SAE.

11.3.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF screen. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE eCRF screen.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF screen.

11.3.3 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF screen. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF screen.

Abnormal laboratory values will be reported as an AE if: the laboratory result requires an adjustment in the study drug(s) or discontinuation of treatment, and/ or laboratory findings require additional testing or surgical intervention, a laboratory result or finding is associated with accompanying symptoms, or a laboratory result is considered to be an AE by the investigator.

11.3.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of disease will be recorded on the "Study Discontinuation" eCRF screen. All other on study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the SCRI Innovations SD.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and Adverse Event screen of the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the eCRF Adverse Event screen. During post-study survival follow-up, deaths attributed to progression of disease will be recorded only on the "After Progressive Disease Follow-Up" eCRF screen.

11.3.5 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolongation of pre-existing hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study), does not require reporting as an SAE to the SCRI Innovations SD.

11.3.6 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History eCRF screen. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an SAE Report Form and/or AE eCRF screen, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.3.7 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria (see Section 11.1.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

11.3.8 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

If a patient becomes pregnant while enrolled in the study or within 3 months after the last dose of study drug, a Pregnancy Form (a paper report form, not available within the eCRF) should be completed and faxed to the SCRI Innovations SD. SCRI Innovations SD should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to SCRI Innovations SD.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to the SCRI Innovations SD immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome. Newborns should be followed for a minimum of 12 weeks.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

If the subject becomes pregnant, the drug will be immediately discontinued. The investigator will discuss the risks and concerns of investigational drug exposure to a developing fetus and counsel the subject and/or pregnant partner (or ensure that such counseling is provided).

SCRI Innovations SD will notify Onyx DS within 24 hours of learning of any pregnancy.

11.3.9 Carfilzomib Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the SCRI Innovations SD no greater than 24 hours from first knowledge of the event using the corresponding screens in the eCRF and following the same process described for SAE reporting (see Section 11.2) if the overdose is symptomatic.

For information on how to manage an overdose of carfilzomib, see the IB.

11.4 Sponsor Serious Adverse Event Reporting Requirements

SCRI Innovations SD will forward SAE information to Onyx Drug Safety and Pharmacovigilance, either via Fax: (800) 783-7954 or via email: Adverse.Events@onyx.com within 1 business day of SCRI Innovations SD personnel becoming aware of the SAE.

SCRI Innovations is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with International Conference on Harmonisation (ICH) guidelines, FDA regulations.

11.4.1 SCRI Innovations Assessment of Unexpected Adverse Events (UAE)

SCRI Innovations SD is responsible for assessing an adverse event or suspected adverse event as "unexpected."

An adverse event or suspected adverse reaction is considered "unexpected" when the following conditions occur:

- Event(s) is not mentioned in the IB (or current US Package Insert)
- Event(s) is not listed at the specificity or severity that has been observed
- An event(s) is not consistent with the General Investigative Plan or in the current application
- Includes AEs or SAR that may be anticipated from the pharmacological properties of the study drug, or that occur with members of the drug class, but that have previously been observed under investigation

When applicable, an unexpected adverse event may also apply to an event that is not listed in the current US Package Insert (USPI) or an event that may be mentioned in the USPI, but differs from the event because of greater severity or specificity.

Known as Suspected Unexpected Serious Adverse Reactions (SUSAR), these events suspected (by the Investigator or Sponsor) to be related to the study drug, are unexpected (not listed in the IB or USPI), and are serious (as defined by the protocol) and require expedient submission to relevant health authorities within 7 days (fatal or life-threatening event) or 15 days (all serious events), or as defined by law. The term SUSAR is used primarily in the reporting of events to regulatory authorities.

Expected AEs are those events that are listed or characterized in the Package Insert or current IB.

11.4.2 SCRI Innovations Reporting for Clinical Studies Under an Investigational New Drug Application

All written IND Safety Reports submitted to the FDA by the SCRI Innovations Safety Department must also be faxed to pharmaceutical company(ies) that are supporting the study with either funding or drug supply:

Onyx Drug Safety and Pharmacovigilance

Contact Information:

Onyx Fax: (800) 783-7954

E-mail: Adverse.Events@onyx.com

12. REGISTRATION ON CLINICALTRIALS.GOV

This study will be registered on ClinicalTrials.gov by the sponsor, SCRI Development Innovations within 21 days of the enrollment of the first patient as required by the Food And Drug Administration Amendments Act of 2007. Updates and changes will be submitted to ClinicalTrials.gov in compliance with regulations. The Primary Completion Date for this study will be the date upon which the last patient undergoes an assessment for response [the primary outcome variable is Overall Response Rate (ORR) which is defined as the proportion of patients with confirmed complete response (CR) or partial response (PR) according to RECIST v1.1 criteria]. Patients will be evaluated for response every 3 cycles. Patients demonstrating an extended period of stable disease will be considered non-responders after 12 cycles of treatment.

Study results will be posted on ClinicalTrials.gov within 12 months of the Primary Completion Date

13. QUALITY ASSURANCE AND QUALITY CONTROL

13.1 Study Monitoring, Auditing, and Inspecting

The investigator will permit study-related monitoring, quality audits, and inspections by SCRI Innovations or its representative(s), government regulatory authorities, and the IRB of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for inspections of applicable study-related facilities. The investigator will ensure that the study monitor or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

At SCRI Innovations discretion, Source Document Verification (SDV) may be performed on all data items or a percentage thereof.

Participation as an investigator in this study implies the acceptance of potential inspection by government regulatory authorities, SCRI Innovations or its representative(s).

14. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

14.1 Institutional Review Board Approval

The clinical study protocol, informed consent form (ICF), IB, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., Principal Investigator payments) and compensation available to the patients and documentation evidencing the Principal Investigator's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the study start.

The Principal Investigator/SCRI Innovations and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going, IRB study review. The Principal Investigator/SCRI Innovations (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by SCRI Innovations or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates for carfilzomib, will be prepared by SCRI Innovations or its representative as required, for distribution to the Investigator(s) and submission to the relevant IRB.

14.2 Regulatory Approval

As required by local regulations, SCRI Innovations will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, SCRI Innovations will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

14.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form (ICF).

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the ICF, to include the patient's signature, will be provided by the investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study should be obtained.

14.3.1 Confidentiality

14.3.1.1 Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws

- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date
- The rights of a research patient to revoke his or her authorization

In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorized representatives of SCRI Innovations, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number and initials will identify patients in the eCRF or other documents submitted to SCRI Innovations. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF. No material bearing a patient's name will be kept on file by Sponsor. Patients will be informed of their rights within the ICF.

14.3.1.2 Investigator and Staff Information

Personal data of the investigators and sub-investigators may be included in the SCRI Innovations database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub investigator, SCRI Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

14.4 Financial Information

The finances for this clinical study will be patient to a separate written agreement between the SCRI Development Innovations, LLC and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

15. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

15.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by SCRI Innovations or its representatives. All amendments require review and approval of all pharmaceutical companies and the Principal Investigator supporting the study. The written

amendment must be reviewed and approved by SCRI Innovations, and submitted to the IRB at the investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, patient number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB of record for the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by SCRI Innovations as applicable, and IRB approval obtained, and specifically when an increase to dosing or patient exposure and/or patient number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment approval from IRB and/or FDA or other regulatory authorities include, but are not limited to, the following:

- Change to study design
- Risk to patient
- Increase to dose or patient exposure to drug
- Patient number increase
- Addition or removal of tests and / or procedures
- Addition/removal of a new Investigator

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the patients, their consent to continue participation in the study should be obtained.

15.2 Documentation Required to Initiate the Study

Before the study may begin certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

SCRI Innovations
Regulatory Department
3322 West End Avenue, Suite 900
Nashville, TN 37203

Documents at a minimum required to begin a study in the US include, but are not limited to, the following:

- A signature-authorized protocol and contract
- A copy of the official IRB approval of the study and the IRB members list
- Current Curricula Vitae for the principal investigator and any associate investigator(s) who will be involved in the study
- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB-approved consent form (and patient information sheet, if applicable) containing permission for audit by representatives of SCRI Innovations, the IRB, and the FDA and other regulatory agencies (as applicable)
- Financial disclosure forms for all investigators listed on Form FDA 1572 (if applicable)
- Site qualification reports, where applicable
- Verification of Principal Investigator acceptability from local and/or national debarment list(s)

15.3 Study Documentation and Storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patient's eCRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patient's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The Principal Investigator and each study staff member is responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or investigator study file [ISF]) of all study-related (essential) documentation, suitable for inspection at any time by

representatives from SCRI Innovations and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed eCRFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain Principal Investigator name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

SCRI Innovations shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation / records of IRB activities as per 21CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from SCRI Innovations or its representative, the investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., eCRFs, medical records), all original, signed ICFs, and copies of all eCRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Sponsor will notify the investigator(s)/institutions(s) when the study-related records are no longer required.

If the investigator relocates, retires, or for any reason withdraws from the study, both SCRI Innovations and its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to SCRI Innovations. The investigator must obtain SCRI Innovations' written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by SCRI Innovations (SCRI Innovations) throughout the study, and will be held by SCRI Innovations at the conclusion of the study.

15.4 Data Collection

The study eCRF is the primary data collection instrument for the study. Case report forms will be completed using the English language and should be kept current to enable SCRI Innovations to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, initials and date of birth will identify the patient in the eCRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to SCRI Innovations and replaced instead with the patient number and patient's initials. The investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested in the eCRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The investigator will electronically sign and date the patient eCRF casebook indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the Principal Investigator, once all data for that patient is final.

15.5 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. SCRI Innovations reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per SCRI Innovations' publication process.

Inclusion of the investigator in the authorship of any multicenter publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the study. The investigator acknowledges that the study is part of a multicenter study and agrees that any publication by the investigator of the results of the study conducted at research site shall not be made before the first multicenter publication. In the event there is no multicenter publication within fifteen (15) months after the study has been completed or terminated at all study sites, and all data has been received, the investigator shall have the right to publish its results from the study, patient to the notice requirements described herein and patient to acknowledgement of SCRI Innovations as appropriate. Investigator shall provide SCRI Innovations thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the study for the purpose only of determining if any confidential or patentable information is disclosed thereby. If SCRI Innovations requests in writing, the investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit SCRI Innovations to seek patent protection and to remove any SCRI Innovations Confidential Information from all publications.

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17. APPENDICES

Appendix A: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death no imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

Appendix B: New York Heart Association (NYHA) Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix C: Guidelines for Female Patients of Childbearing Potential and Fertile Male Patients

Acceptable Contraception Methods:

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 3 months after stopping treatment.

Highly effective contraception is defined as either:

True Abstinence When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Sterilization When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

Male Partner Sterilization When the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.

Use of a combination of any two of the following (one from a + one from b):

a) Placement of an intrauterine device (IUD) or intrauterine system (IUS)

b) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of child-bearing potential must use condoms plus spermicidal agent during the study treatment period and for 3 months after the last dose of study drug, and should not father a child during this period.

Male patients must also refrain from donating sperm during their participation in the study.

The following are acceptable forms of barrier contraception:

- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository

Unacceptable Contraception Methods: for women of childbearing potential include:

- IUD progesterone T
- Female condom

- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Pregnancies

To ensure subject safety, each pregnancy in a subject on study treatment must be reported to the SCRI Innovations Safety Department within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or new born complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to **SCRI Innovations Safety Department**. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women Not of Childbearing Potential are defined as Follows:

- Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms).
- Women who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
- Women who are >45 years-of-age, not using hormone-replacement therapy and who have experienced total cessation of menses for at least 12 months OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (140 pmol/L).
- Women who are >45 years-of-age, using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone-replacement therapy.

Appendix D: Schedule of Assessments

ASSESSMENTS	Pre-Treatment	STUDY TREATMENT (*Cycles repeated every 28 days*)							FOLLOW-UP
	Baseline[a]	Day 1	Day 2	Day 8	Day 9	Day 15	Day 16	End of Study Evaluation[m]	Prior to disease progression[n]
Tests and Observations									
Informed consent	X								
Medical history	X							X	X
Physical exam[b]	X	X						X	X
Vital Signs[c]	X	X	X	X	X	X	X	X	
ECOG PS	X	X		X		X		X	
12-lead ECG	X								
ECHO[d]	X								
Adverse event evaluation		X	X	X	X	X	X	X	
Concomitant medication review	X	X	X	X	X	X	X	X	
Survival status									
Laboratory Assessments									
CBC, 3-part differential, and platelets	X	X		X		X		X	X
CMP [e]	X	X		X		X		X	X
PT, PTT, INR[f]	X								
Serum or Urine Pregnancy Test[g]	X							X	
Archival Tumor Tissue Samples	X[h]								
Fasting serum chromagranin A[i]	X[i]	X[i]							
24 hour urine for 5-HIAA[j]		X[j]							X
Staging (Every 3 cycles)									
CT Scan chest[k]	X							X	X
CT Scan abdomen /pelvis[l]	X							X	X

Appendix D: Schedule of Assessments (continued)

a Baseline procedures including medical history, physical examination, peripheral neuropathy assessment, 12-lead ECG, ECOG PS, CBC, CMP, PT/PTT/INR, and serum or urine pregnancy test should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated. Scans should be performed ≤ 28 days prior to initiation of treatment, to document measurable or evaluable disease.

b Physical examination will include measurements of height (pre-treatment visit only), weight, and vital signs.

c Vital signs will include resting heart rate, blood pressure, respiratory rate, and temperature.

d ECHO with calculated LVEF (repeat if/when clinically indicated). MUGA is acceptable if ECHO is not available.

e CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO^2, ALP, AST, ALT, total bilirubin, total protein, and albumin.

f If PT/PTT/INR are normal at baseline they do not need to be repeated. Patients requiring the initiation of an anti-coagulation therapy during study treatment should have coagulation tests performed according to standard practice guidelines.

g Serum or urine pregnancy tests are to be conducted in women of childbearing potential at the beginning of the study and at the end of study visit or 30 days post last dose..

h If available, archival tissue samples will be requested by study site personnel.

i Fasting (overnight) serum chromagranin A test will be done during screening and then on Day 1 of each cycle.

j 24 hour urine for 5-HIAA will be done during screening and then every 3 cycles to assess response.

k CT scans of the chest ≤4 weeks prior to initiation of treatment and then every 3 cycles during the treatment and at the end of study visit, if no PD and not done within prior 6 weeks.

l CT scans of the abdomen/pelvis ≤4 weeks prior to initiation of treatment and then every 3 cycles during the treatment and at the end of study visit.

m Patients should visit the study center ≤30 days for end-of-treatment assessments. Patients must be followed for AEs for 30 calendar days after the last dose of study drug.

n Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 3 months (±1 month) from the date of last dose of study drug until disease progression. PFS will be evaluated for this trial 6 and 12 months after the last patient is enrolled. No follow up will be done for survival or if the patient starts a subsequent therapy.

Appendix E: Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Definitions

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al 2009). Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

Baseline Eligibility

Measurable Disease:	**Tumor lesions:** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: • 10 mm by CT by computerized tomography (CT scan slice thickness no greater than 5 mm). • 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable). • 20 mm by chest x-ray. **Skin lesions:** Documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Disease:	All other lesions, including small lesions (longest diameter <<10 mm or pathological lymph nodes with ≥10- to <<15-mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses, abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
Target Lesions:	The most reproducible measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), should be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and that may be identified as target lesions must meet the criterion or a short axis of ≥15 mm by CT scan. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor response.
Non-Target Lesions:	**All other lesions should be identified as non-target lesions at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.**

Guidelines for Evaluation of Measureable Disease

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment, as per protocol screening requirements.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical Lesions:	Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm in diameter. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest X-ray:	Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, a CT scan is preferable.
Conventional CT and MRI:	CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).
Ultrasound:	When the primary study endpoint is objective response, ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound may also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
Endoscopy and Laparoscopy:	Use of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Therefore, use of these techniques for objective tumor response should be restricted to validation purposes in specialized centers. Such techniques can be useful in confirming complete pathological response when biopsies are obtained.
Tumor Markers:	Tumor markers alone cannot be used to assess response. If markers are initially above the upper limit of normal, they must normalize for a subject to be considered in complete clinical response when all lesions have disappeared.
Cytology and Histology:	Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Response Criteria

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters..
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum of diameters since the treatment started.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest (nadir) sum since the treatment started, or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes must be non-pathological in size (<<10 mm short axis).
Stable Disease (SD):	Persistence of one or more non-target lesions and/or persistence of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. When the subject also has measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Confirmation of response (by repeat scans after 4 weeks or as specified in the protocol) is required for studies in which response rate is the primary endpoint, but is not required in randomized studies or studies with primary survival endpoints (i.e., where response is not a primary endpoint).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	NO	CR
CR	SD	NO	PR
CR	NE	NO	PR
PR	SD OR NE	NO	PR
SD	SD OR NE	NO	SD
PD	ANY	YES OR NO	PD
ANY	PD	YES OR NO	PD
ANY	ANY	YES	PD

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of a CR depends upon this determination, it is recommended that the residual lesion be investigated by fine needle aspirate or biopsy to confirm the CR status.

When nodal disease is included in the sum of target lesions, and the nodes decrease to "normal" size (<<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression, should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of "zero" on the eCRF.