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Title: A Phase II Trial of Mutation-Targeted Therapy with Sunitinib or Everolimus in Patients with Advanced Low-or Intermediate Grade Neuroendocrine Tumors of the Gastrointestinal Tract and Pancreas

NCI Principal Investigator: Naris Nilubol, MD
Surgical Oncology Program (SOP)
Bldg. 10-CRC Room 4-5932
10 Center Drive
Bethesda, MD 20892
Phone: 240-760-6154
Email: naris.nilubol@nih.gov

Investigational Agents: None

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Précis

Background:

- Neuroendocrine tumors (NETs) of the gastrointestinal tract and pancreas are a rare and heterogeneous group of neoplasms with unique tumor biology, natural history, and clinical management issues.
- Most NETs are sporadic, but they can be part of familial cancer syndromes such as multiple endocrine neoplasia type 1 (MEN1), neurofibromatosis type 1 (NF1) or Von Hippel-Lindau (VHL) syndrome.
- Well-differentiated, low or intermediate grade NETs have a heterogeneous natural history.
- Surgery is the only curative treatment option in patients with localized early stage NETs.
- The optimal management strategy for patients with advanced NETs is unknown.
- The majority of NETs have somatic mutations in *MEN1* and *CDKN1B*, and genes involved in the *PI3K*/*AKT*/*mTOR* signaling pathway, and/or overexpression of growth factors and their receptors such as *VEGF*, *VEGFR*, *PDGF*, and *PDGFR* that can be targeted for therapy.
- Survival in patients with NETs and somatic mutations is better than patients with wildtype NETs.
- Sunitinib (multi-tyrosine kinase inhibitor) and everolimus (mTOR signaling pathway inhibitor) are currently approved for the treatment of progressive, unresectable, locally advanced or metastatic pancreatic NETs.
- However, mutation targeted therapy with sunitinib or everolimus has not been studied in this patient population.
- The present proposal aims to determine if mutation targeting therapy for patients with advanced low- or intermediate grade NETs is more effective than historically expected results.

Objectives:

- To determine the progression-free survival in patients with NETs of the gastrointestinal tract and pancreas treated with sunitinib or everolimus based on tumor genotyping.

Eligibility:

- Patients with:
    - progressive, histologically or cytologically diagnosed low or intermediate grade locally advanced or metastatic NETs.
    - Age ≥ 18 years

Design:

- Phase II open labeled clinical trial.
- Tumor biopsy for tumor genotyping will be performed if the patient does not have archival tissue available and does not have MEN1, VHL or NF1.

- Patients with somatic or germline mutations in *MEN1/PDGFR*/*KIT*/FMS-like tyrosine kinase-3 will be treated with sunitinib (Arm 1).
- Patients with somatic/germline mutations in *NF1/PTEN/PI3K/AKT/mTOR/VHL* will be treated with everolimus (Arm 2).
- Patients with wildtype tumor will be treated with sunitinib (Arm 1).
- Patients who have disease-progression on either sunitinib or everolimus will cross-over to the other drug.
- Treatment will continue until disease progression, unacceptable toxicity, or consent withdrawal.
- Up to 120 patients will be accrued to the study. It is anticipated that 20-30 patients per year may enroll into this trial; thus, accrual may be completed in 4-5 years.

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective:

- To determine the progression-free survival (PFS) on first-line therapy in patients with NETs of the gastrointestinal tract and pancreas treated with sunitinib or everolimus based on tumor genotyping.

1.1.2 Secondary Objectives:

- To determine overall response rate (ORR; i.e., sum of complete response [CR], partial response [PR], and stable disease [SD]) and duration of response
- To determine overall survival and median survival time (MST)
- To evaluate any relationship between tumor genotype, treatment and PFS
- Safety endpoints (i.e. AEs, clinical laboratory evaluations, ECGs, physical examination findings, and vital sign measurements).

1.2 BACKGROUND AND RATIONALE

1.2.1 Neuroendocrine tumors

Neuroendocrine tumors (NETs) of the gastrointestinal tract and pancreas are a rare and heterogeneous, but clinically important group of neoplasms with unique tumor biology, natural history, and clinical management issues[1-4]. NETs arise in the disseminated neuroendocrine cells of the gastrointestinal tract (GI) mucosa (also called "carcinoids") and the pancreatic islet cells. Approximately 85% of NETs are sporadic and the remainder occur as part of familial cancer syndromes including multiple endocrine neoplasia-type 1 (MEN1), von Hippel–Lindau disease (VHL), von Recklinghausen's disease (neurofibromatosis 1, NF-1), and tuberous sclerosis (TS)[5-9].

Neuroendocrine cells are one of the largest group of hormone-producing cells in the body. At least 13 distinct gut neuroendocrine cells exist, all of which may oversecrete various bioactive peptides or amines including serotonin, somatostatin, histamine, and gastrin, which can result in significant morbidity and mortality. Up to 20% of patients with NETs may develop carcinoid syndrome associated with flushing, abdominal pain, diarrhea, bronchoconstriction, and carcinoid heart disease[10].

A unique feature of most NETs is the expression of somatostatin receptors (SSTR) by the tumor cells. There are five different SSTR subtypes; more than 80% of NETs of both the GI tract and pancreas express multiple subtypes, with a predominance of receptor subtypes 2 and 5[11-14]. Somatostatin is an endogenous SSTR agonist which inhibits the secretion of a broad range of hormones from the endocrine system, including serotonin, insulin, glucagon, and gastrin[15]. Somatostatin analogs have limited clinical use due to its short half-life (<3 min); however, long-acting somatostatin analogues play a central role in the treatment of hormonal symptoms produced by NETs but do not have significant antitumor activity[13, 16].

Epidemiology

The annual incidence of NETs has been increasing in the United States and worldwide[2, 7, 17-20]. Whereas early studies have reported incidences of < 1 per 100,000 persons per year[21-23], recent age-adjusted epidemiologic studies have shown a significant, more than five-fold, increase in NETs incidence from 1973 to 2005[7, 18-20, 24]. Based on data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) cancer registry, the annual incidence of NETs was estimated to be 7.8 per 100,000 persons in 2013[7]. The prevalence of NETs has been estimated as 35 per 100,000 and may be considerably higher if clinically "silent" tumors are included[25].

Classification

NETs are generally classified into functioning (hormone hypersecreting) or nonfunctioning (clinically "silent") tumors, based on their ability to produce hormone-associated symptoms. However, other classification systems with many common themes, such as the distinction of well-differentiated (low and intermediate-grade) from poorly differentiated (high-grade) NETs and the prognostic significance of proliferative rate index have been used over the past 5 decades (**Table 1**). In general, well-differentiated, low or intermediate grade NETs have a relatively indolent behavior with slow progression but poorly differentiated tumors may exhibit highly aggressive behavior with a rapid metastatic spread that is clinically indistinguishable from pancreatic adenocarcinoma or small-cell lung cancer[5, 7, 26]. Fortunately, poorly differentiated tumors account for only a small subset of all NETs.

Recent large, epidemiologic studies have shown that majority of NETs (60-90%) are clinically non-functioning, well-differentiated, slow-growing neoplasms diagnosed, in most instances, incidentally during an unrelated procedure[2, 6, 10, 13, 27-29]. As a result of this insidious biological behavior, many patients with NETs have advanced disease at diagnosis, with regional or distant metastasis observed in more than 50% of patients[13, 20].

Table 1:. Nomenclature and Classification of Neuroendocrine Tumors

Differentiation & Grade	Mitotic Count (/10 HPF)[a]	Ki-67Index (%)[b]	Traditional Classification	ENETS/WHO Classification	Moran et al[30]
Well differentiated					
Low grade (grade 1)	< 2	≤ 2	Carcinoid, islet cell, PNET	Neuroendocrine tumor, grade 1	Neuroendocrine carcinoma, grade 1
Intermediate grade (grade 2)	2-20	3-20	Carcinoid, atypical carcinoid[c], islet cell, PNET	Neuroendocrine tumor, grade 2	Neuroendocrine carcinoma, grade 2
Poorly differentiated					
High grade (grade 3)	> 20	> 20	Small-cell carcinoma	Neuroendocrine carcinoma, grade 3, small cell	Neuroendocrine carcinoma, grade 3, small cell
			Large-cell neuroendocrine carcinoma	Neuroendocrine carcinoma, grade 3, large cell	Neuroendocrine carcinoma, grade 3, large cell

Abbreviations: HPF, high-power field; ENETS, European Neuroendocrine Tumor Society; PNET, pancreatic neuroendocrine tumor.
a HPF = 2 mm^2; at least 40 fields (at ×40 magnification) were evaluated in areas of highest mitotic density. Cutoff values were taken from American Joint Committee on Cancer staging system (seventh edition).
b Ki67/MIB1 antibody; percentage of 2,000 tumor cells in areas of highest nuclear labeling. Cutoff values were taken from American Joint Committee on Cancer staging system (seventh edition).
c The term atypical carcinoid only applies to intermediate-grade neuroendocrine tumor of the lung.

Prognosis

Even though there has been a significant improvement in the diagnosis and management of NETs, no significant change in survival has been observed over the last 30 years[6, 7]. Reported survival times for patients with advanced NETs in population-based and institutional series are highly variable likely due to variability in tumor biology, classification, treatment modalities, and patient selection. According to data from the SEER database, the median overall survival (OS) for patients with metastatic NETs was two years[20], whereas in a large institutional database, the median OS for a similar group of patients was 5.8 years[31]. According to the European Neuroendocrine Tumor Society (ENETS) consensus statement, the median OS of nonfunctional NETs was 38 months with a 5-year survival rate of 43%[32].

Management of advanced NETs

Advanced NETs are characterized by local invasion, and regional and distant metastases. While the treatment of localized NETs is surgical resection, a variety of therapeutic options are available for patients with advanced NETs. These include medical control of excess hormone levels and associated symptoms, cytoreductive surgery for patients with advanced disease, radioembolization, chemoembolization, systemic chemotherapy, interferon, long-acting somatostatin analogs, receptor-targeted radionuclide therapy, and or liver transplantation[33-36]. When to apply a given option, what combination therapeutic approach should be used, how long treatment should be continued, and in what subgroup of patients a particular treatment option should be used is unclear and controversial[37].

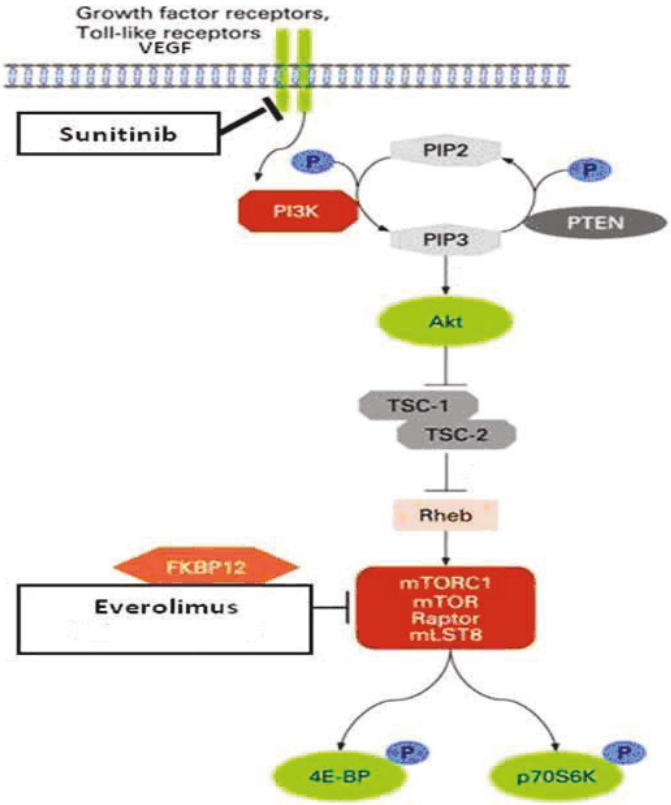
When feasible, aggressive surgical resection has been associated with the best symptom-free and long-term survival results in patients with advanced NETs[6, 38-46]. Despite the lack of randomized control data, a recent consensus statement from the ENETS emphasized that resection should be the first-line treatment option for patients with advanced NETs if up to 90% of the disease burden is resectable[47]. However, only 5% to 20% of patients with advanced NETs meet this “conventional” criterion[43, 48]. Furthermore, a significant number of patients undergoing debulking surgery will have residual disease and recurrence rates are high[49]. Thus, it is becoming increasingly clear that combination (surgical and medical) therapeutic strategies to improve the outcomes of patients with advanced NETs need to be explored.

Mutation-targeted therapy

Our understanding of the genetic changes associated with sporadic and familial NETs has improved considerably over the last 3 decades. Driver oncogene and tumor suppressor genes have been identified in most NETs[50-56]. Overall, the majority of NETs will have somatic mutations in *MEN1*, the phosphatidylinositol 3-kinase (*PI3K)/AKT/* mammalian target of rapamycin (*mTOR*) signaling pathway[20, 57-61], and or overexpression of growth factors and their receptor such as vascular endothelial growth factor (*VEGF*), *VEGF* receptor (*VEGFR*), platelet-derived growth factor (*PDGF*), and *PDGF* receptor (*PDGFR*) (**Figure 1**)[62-65]. The most common mutations (somatic and germline for familial cancer syndromes) are in *MEN1*,

VHL, *DAX*, *ATRX*, *TP53* and *CDKN1B*. These mutations are present in 87% of pancreatic neuroendocrine tumors and in 60% of gastrointestinal neuroendocrine tumors.

Figure 1. Signaling pathways commonly activated in NETs.



mTOR pathway in NETs

Several studies, using whole exome-sequencing and expression profiling, have consistently identified somatic mutations implicating the *mTOR* pathway as a common event in NETs (**Figure 1**)[57-59, 61, 63]. The *mTOR* pathway has a central role in cancer cell growth, proliferation, differentiation, and apoptosis. Tuberous sclerosis 2 (*TSC2*), phosphatase and tensin homolog (*PTEN*), *PIK3CA*, and fibroblast growth factor 13 (*FGF13*) are among the key modulators of the *mTOR* pathway[52, 56]. Several studies of global gene expression profiling in a large panel of pancreatic NETs showed that *TSC2* gene and *PTEN* gene were downregulated in most tumors, and their low expression was significantly associated with shorter disease-free and overall survival[59, 66]. In addition, expression of *FGF13* was significantly associated with liver metastasis and shorter disease-free survival[59, 66]. A recent whole-exome sequencing study also revealed the presence of somatic mutations in *MEN1, DAXX, ATRX, TSC2, PTEN*, and *PIK3CA* genes in the majority of s of sporadic pancreatic NETs[58]. Moreover, the presence of these mutations was associated with better survival when compared to patients with NETs, which had wild type *MEN1,* and/or *DAXX/ATRX*[58].

Activation of the *mTOR* pathway has also been implicated in several familial cancer syndromes (TS, NF-1, and VHL) associated with the development of NETs[20, 51, 59, 66-68]. Findings of these and other studies further support the critical role of the *mTOR* pathway in NETs and adds to the wealth of data that has spurred the clinical development of mTOR inhibitors as a treatment option for patients with advanced NETs (**Table 2**).

Key drivers of angiogenesis: growth factors and their receptors in NETs

The highly vascular nature of NETs led to initial interest in investigating neoangiogenesis in NETs. A number of studies have found elevated expression of several cellular growth factors and their receptors in NETs; *VEGF*, *VEGF* receptor (*VEGFR*), platelet-derived growth factor (*PDGF*), *PDGF* receptor (*PDGFR*), and stem cell factor receptor (*c-KIT*), and epidermal growth factor receptor (EGFR)[62-65, 69, 70]. Many of these receptors with their respective growth factor ligands function as tyrosine kinases (TKs) directly and indirectly regulating tumor growth, survival and angiogenesis. The hypothesis that inhibiting these targets in concert will result in broad antitumor efficacy in patients with NETs has been studied in several clinical trials (**Table 2**).

Table 2. Phase II and III Trials in advanced NETs

Study tumor type and Regimen	Total No. of Patients	ORR (%)	Median PFS (months)	Median TTP (months)	Criteria	*P*
PNETs						
Moertel et al[35]	105					
Streptozocin + Doxorubicin		69		20.0	NS	.001
Streptozocin + Fluorouracil		45		6.9		
Raymond et al[53]	171					
Sunitinib		9		11.4	RECIST	< .001
Placebo		0		5.5		
Yao et al[55]	410					
Everolimus			11.0		RECIST	< .001
Placebo			4.6			
Carcinoid tumors						
Rinke et al[71]	90					
Octreotide LAR		2		14.3	WHO	< .001
Placebo		2		6.0		
Pavel et al[72]	429					
Everolimus + octreotide LAR			16.4		RECIST	.026
Placebo + octreotide LAR			11.3			
Kulke et al[63]						
Sunitinib	41	2.4		10.2	RECIST	

Abbreviations: PNETs, pancreatic neuroendocrine tumors; ORR, overall response rate; PFS, progression-free survival; TTP, time to progression; RECIST, Response Evaluation Criteria in Solid Tumors; LAR, long-acting release; NS, Nonstandard (includes computed tomography scan, radioisotope scan, physical exam, or hormonal response)

1.2.2 Everolimus

Everolimus is a novel derivative of rapamycin. It has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation. Everolimus is approved in Europe and other global markets (trade name: Certican®) for cardiac and renal transplantation, and in the United States (trade name: Zortress®) for the prevention of organ rejection of kidney transplantation.

Afinitor® was approved for adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib in 2009. In 2010, Afinitor® received United States (US) approval for patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC). Everolimus is also available as Votubia® in the European Union (EU) for patients with SEGA associated with TSC who require therapeutic intervention but are not candidates for curative surgical resection. Afinitor® was approved for "progressive pancreatic neuroendocrine tumor (PNET) in patients with unresectable, locally advanced, or metastatic disease" in 2011 in various countries, including the US and Europe. In 2012 Afinitor® received approval for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2- negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. Furthermore, in 2012, Afinitor® received approval for the treatment of patients with TSC who have renal angiomyolipoma not requiring immediate surgery.

Everolimus acts as a signal transduction inhibitor. Everolimus selectively inhibits mTOR (mammalian target of rapamycin), specifically targeting the mTOR-raptor signal transduction complex. mTOR is a key serine-threonine kinase in the PI3K/AKT signaling cascade, which is known to be dysregulated in a wide spectrum of human cancers[73].

Everolimus is being investigated as an anticancer agent based on its potential to act

- directly on the tumor cells by inhibiting tumor cell growth and proliferation;
- indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell VEGF (vascular endothelial growth factor) production and VEGF-induced proliferation of endothelial cells).

1.2.2.1 mTOR pathway and everolimus

At the cellular and molecular level, everolimus acts as a signal transduction inhibitor. It selectively inhibits mTOR (mammalian target of rapamycin), a key protein kinase which regulates cell growth, proliferation and survival. The mTOR kinase is mainly activated via the phosphatidylinositol 3-kinase (PI3-Kinase) pathway through AKT/PKB and the tuberous sclerosis complex (TSC1/2). Mutations in these components or in PTEN, a negative regulator of PI3-kinase, may result in their dysregulation. Abnormal functioning of various components of the signaling pathways contributes to the pathophysiology of numerous human cancers. Various preclinical models have confirmed the role of this pathway in tumor development[74].

1.2.2.2 Non-clinical experience

Everolimus inhibits the proliferation of a range of human tumor cell lines *in vitro* including cell lines originating from lung, breast, prostate and colon cancer, melanoma and glioblastoma. IC50s range from sub/low nM to μM. Everolimus also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS) *in vitro*, with particular potency against VEGF-induced proliferation suggesting that everolimus may also act as an anti-angiogenic agent. The anti-angiogenic activity of everolimus was confirmed *in vivo*. Everolimus selectively inhibited VEGF-dependent angiogenic response at well tolerated doses. Mice with primary and metastatic tumors treated with everolimus showed a significant reduction in blood vessel density when compared to controls *(*Everolimus Investigator's Brochure, 2013).

The potential of everolimus as an anti-cancer agent was shown in rodent models. Everolimus is orally bioavailable, residing longer in tumor tissue than in plasma in a subcutaneous mouse xenograft model, and demonstrating high tumor penetration in a rat pancreatic tumor model. The pharmacokinetic profile of everolimus indicates sufficient tumor penetration, above that needed to inhibit the proliferation of endothelial cells and tumor cell lines deemed sensitive to everolimus *in vitro (*Everolimus Investigator's Brochure, 2013).

Everolimus administered orally daily was a potent inhibitor of tumor growth, at well tolerated doses, in 11 different mouse xenograft models (including pancreatic, colon, epidermoid, lung and melanoma) and two syngeneic models (rat pancreatic, mouse orthotopic melanoma) *(*Everolimus Investigator's Brochure, 2013). These models included tumor lines considered sensitive and "relatively resistant" *in vitro*. In general, everolimus was better tolerated in mouse xenograft models than standard cytotoxic agents (i.e., doxorubicin and 5-fluorouracil), while possessing similar anti-tumor activity. Additionally, activity in a VEGF-impregnated subcutaneous implant model of angiogenesis and reduced vascularity (vessel density) of everolimus-treated tumors (murine melanoma) provided evidence of *in vivo* effects of angiogenesis *(*Everolimus Investigator's Brochure, 2013).

It is not clear which molecular determinants predict responsiveness of tumor cells to everolimus. Molecular analysis has revealed that relative sensitivity to everolimus *in vitro* correlates with the degree of phosphorylation (activation) of the AKT/PKB protein kinase and the S6 ribosomal protein; in some cases (i.e., glioblastoma) there is also a correlation with PTEN status *(*Everolimus Investigator's Brochure, 2013).

In vivo studies investigating the anti-tumor activity of everolimus in experimental animal tumor models showed that everolimus monotherapy typically reduced tumor cell growth rates rather than produced regressions. These effects occurred within the dose range of 2.5 mg to 10 mg/kg, orally once a day *(*Everolimus Investigator's Brochure, 2013).

All significant adverse events observed in toxicology studies with everolimus in mice, rats, monkeys and mini-pigs were consistent with its anticipated pharmacological action as an anti-proliferative and immunosuppressant and at least in part reversible after a 2 or 4-week recovery period with the exception of the changes in male reproductive organs, most notably testes.

In vitro genotoxicity studies covering relevant genotoxicity end-points showed no evidence of clastogenic or mutagenic activity.

In male fertility studies in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count and plasma testosterone levels were diminished at 5 mg/kg

which corresponded to 0.7 times the estimated clinical exposure at 10 mg/day, and caused a decrease in male fertility. There was evidence of reversibility. Female fertility was not affected, but everolimus caused an increase of pre-implantation loss in female rats at doses > 0.1 mg/kg, suggesting it could also potentially impact fertility in females. Everolimus crossed the placenta and was toxic to the conceptus. In rats, everolimus caused embryo/fetotoxicity at systemic exposure below the planned therapeutic level comprising mortality and reduced fetal weight. The incidence of skeletal variations and malformations at 0.3 and 0.9 mg/kg (e.g. sternal cleft) was increased. In rabbits, embryo toxicity was evident by an increase in late resorptions. Effects of everolimus on the pre- and postnatal development of rats were limited to slightly affected body weight and survival in the F1-generation at ≥0.1 mg/kg, and did not indicate a specific toxic potential.

The potential reproductive risk for humans is unknown. However, due to the observed malformations in rats, everolimus should be considered potentially teratogenic. Everolimus should not be given to pregnant women unless the potential benefit outweighs the potential risk for the fetus. Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving everolimus and up to 8 weeks after treatment has been stopped. It is not known whether everolimus is excreted in human milk. In animal studies, everolimus and/or its metabolites were readily transferred into the milk of lactating rats. Therefore women who are taking everolimus should not breastfeed.

1.2.2.3 Clinical Experience

1.2.2.3.1 Phase 1 Studies

In a phase 1 dose escalation study of 92 patients which evaluated both daily and weekly doses, the maximum tolerated doses for everolimus monotherapy were determined to be 70 mg/week and 10 mg/day. In another dose escalation study of 55 subjects, again evaluating both daily and weekly doses, the MTDs were determined to be 50 mg/week or 10 mg/day. In this study, data suggested that a dose greater than or equal to 10 mg/day was required for complete inhibition of the downstream effectors of mTOR. Based on these results, monotherapy everolimus doses of 10 mg/day and 70 mg/week were recommended for Phase II and III studies. Daily doses provided more complete suppression than weekly dosing[75]. Results from a Japanese Phase I study confirmed that everolimus 10 mg/day was the optimum daily monotherapy dose to implement in pivotal studies in Japan.

1.2.2.3.2 Phase 2 NET studies

A phase II trial of everolimus in combination with long-acting octreotide in patients with advanced low- to intermediate-grade NETs (30 carcinoid and 30 islet cell tumors) demonstrated a partial response rate of 20% and median progression-free survival (PFS) of 15 months[76]. A follow up phase II trial, which randomized patients with metastatic pancreatic NETs (who experienced progression on or after chemotherapy) to everolimus or everolimus in combination with long-acting octreotide showed a significantly longer median PFS in patients receiving combination therapy as compared to everolimus alone (16.7 months versus 9.7 months)[77]. Most recently, a multicenter double-blind placebo-controlled phase III trial (RADIANT-3) comparing everolimus to placebo in 410 patients with progressive, advanced low- or intermediate-grade NETs showed that median PFS was improved with everolimus (11.0 months versus 4.6 months)[55]. The results of these studies have led to the approval of everolimus by the FDA for the treatment of progressive, unresectable, locally advanced or metastatic, low- or

intermediate grade PNETs. Unfortunately, none of these clinical trials evaluated what pathways or genes were altered in patient tumor samples.

1.2.3 Sunitinib

Sunitinib malate is a small molecule kinase inhibitor with activity against a number of tyrosine kinase receptors, including *VEGFR*, *PDGFR*, *KIT*, *RET*, and FMS-like tyrosine kinase-3 (*FLT3*)[78, 79]

Mechanism of Action

Tumor VEGF expression has been associated clinically with disease prognosis in many different types of malignancies. VEGF expression is increased by diverse stimuli including proto-oncogene activation and hypoxia, with the hypoxic state frequently arising in solid tumors because of inadequate perfusion. In addition to its angiogenic role, VEGF also profoundly increases the permeability of the vasculature thereby, potentially contributing to tumor progression. A leaky tumor endothelium enhances nutrient and catabolite exchange and represents less of a barrier to tumor cell migration and intravasation during metastasis. Two high-affinity receptors for VEGF with associated tyrosine kinase (TK) activity have been identified in human vascular endothelium; VEGFR-1/Flt-1 and VEGFR-2/kinase insert domain-containing receptor (KDR). Although the relative contributions of KDR and Flt-1 signaling in mediating tumor progression have not been clearly elucidated, a number of studies suggest that KDR performs a predominant role.

In addition to VEGF receptor signaling, increasing evidence implicates PDGFR signaling in tumor angiogenesis. Recent nonclinical evidence suggests that inhibition of PDGFR signaling augments the antitumor and anti-angiogenic effects of VEGFR inhibitors. In addition, PDGF signaling is implicated in the autocrine growth of tumor cells and in the recruitment and regulation of tumor fibroblasts.

Upon chronic oral dosing, sunitinib is expected to inhibit PDGF- and VEGF-driven angiogenesis and as a consequence, limit solid tumor growth. Because angiogenesis is necessary for the growth and metastasis of solid tumors, and VEGF is believed to have a pivotal role in this process, sunitinib treatment may have broad-spectrum clinical utility[80, 81]. Sunitinib also exerts direct antitumor activity on cells that express target receptor tyrosine kinases (RTKs) associated with tumor cell proliferation, such as KIT, PDGFR, and RET.

1.2.3.1 Non-clinical Experience

1.2.3.1.1 Specificity and Efficacy Studies

Non-clinical data from *in vitro* and *in vivo* studies have demonstrated sunitinib selectively inhibits the Class 3 and Class 5 RTKs, including receptors for VEGF (VEGFR), KIT, FLT-3, and PDGFR (Investigator's Brochure, 2014). Specifically, receptor phosphorylation inhibition studies have shown that sunitinib inhibits KIT-ligand-induced phosphotyrosine levels in a dose-dependent manner with IC_{50} values of 0.001-0.01 mcM *in vitro* and reduced PDGFR-β phosphotyrosine levels *in vivo*[82]. Sunitinib also selectively inhibited proliferation of human umbilical vein endothelial cells (HUVEC) stimulated with VEGF (IC_{50}=0.04 mcM) compared to FGF-stimulated proliferation (IC_{50}=0.7 mcM)[78].

In animal efficacy studies, sunitinib showed broad antitumor activity in mouse xenograft models against a variety of human tumor cell lines including colorectal cancer (HT-29, Colo205), non-small cell lung cancer (H460), breast cancer (MDA-MB-435), melanoma (A375), epidermoid cancer

(A431), and glioma (SF763T)[78]. Sunitinib has also demonstrated antitumor activity against other breast cancer models (MMTV-v-Ha-ras transgenic mouse mammary carcinoma and dimethylbenzanthracene [DMBA]-induced rat mammary carcinomas)[83]. In an animal model of KIT-expressing small cell lung cancer (SCLC; NCI-H526), sunitinib administration resulted in greater tumor growth inhibition than did imatinib[82].

Combination studies of sunitinib with docetaxel, 5-fluorouracil (5-FU), or doxorubicin resulted in significantly enhanced growth inhibition of human MX-1 breast cancer xenografts compared to levels of inhibition with either sunitinib or the cytotoxic agent alone[83]. Moreover, the combination therapies each led to a significantly increased survival compared to either single agent alone[83]. Significantly delayed tumor growth has also been demonstrated in combination studies of sunitinib and cisplatin in NCI-H526 SCLC xenografts[82].

1.2.3.1.2 Toxicology Studies

Single- and multiple-dose toxicology studies were conducted in mice, rats, rabbits, dogs, and monkeys (Sunitinib Investigator's Brochure, 2014). The acute oral maximally-tolerated dose (MTD) for mice, rats, and dogs was greater than the maximum dose of 500 mg/kg. The MTD in monkeys was greater than the 1200 mg/kg maximum dose tested, but emesis occurred at doses ≥50 mg/kg. Treatment-related effects in the lymphoid tissue, bone marrow, adrenal glands, and bone growth plate were seen in rat repeated-dose studies with gastrointestinal tract, reproductive organ, kidney, pancreas, and pituitary effects reported at the highest dose. Death was observed at the highest dose level of 240 mg/kg/day. Gastrointestinal disturbances (diarrhea, loss of appetite, emesis) as well as hematologic disturbances also occurred in an 8-week study in female monkeys. Other toxicities seen in monkeys included mild elevations in AST, ALT, and creatinine kinase (CK), adrenal gland cortex hemorrhage, acinar degranulation of the salivary glands, decreased erythropoiesis in the bone marrow, and lymphoid atrophy. Possible impairment of immune function in the highest dose group was manifested as cytomegalovirus and bacterial infections.

There is an indication that repeated high doses of sunitinib may lead to cardiac function/contractility changes as confirmed by altered ECG and MUGA or echocardiographic parameters and increased cardiac Troponin I and/or T in single animals that died or were euthanized early due to a moribund condition. These changes appear to be primarily functional and reversible. Due to the poor clinical condition of these animals, it appears that the cardiac changes were not a direct result of sunitinib treatment, but rather resulted from an important, non-compensated volume loss and additional suppression of heart function due to chronotropic incompetence and possible myocardial involvement of uncertain etiology. Data from this study indicate that functional cardiac changes were induced primarily at the highest dose of sunitinib.

Sunitinib was found to be negative for genotoxicity *in vivo* and *in vitro* (Sunitinib Investigator's Brochure, 2014). Wound-healing studies showed a subtle transient delay in skin wound healing in mice treated continuously for up to 5 weeks with supratherapeutic doses of sunitinib at 80 mg/kg/day. However, it was determined that this alteration in wound healing has minimal biologic significance (Sunitinib Investigator's Brochure, 2014).

1.2.3.1.3 Pharmacokinetics

Single-dose pharmacokinetics (PK) was evaluated in mice, rats, at oral doses of 20, 40, 80, and 160 mg/kg (Investigator's Brochure, 2014). At these doses, the respective T_{max} values were 3, 3, 0.5, and 6 hours respectively, while maximum plasma concentration (C_{max}) values were 420,

708, 877, and 1670 ng/mL, respectively. In monkeys, $t_{1/2}\alpha$ and $t_{1/2}\beta$ at a dose of 6 mg/kg PO were 18 and 16 hours, respectively. Repeat-dose PK studies indicated that increases in exposure were not consistently proportional to dose. Steady state plasma concentrations were reached after 28 days of dosing with little change in levels thereafter. Sunitinib appeared to readily distribute into the CNS in mice and to a lesser extent in rats and monkeys.

Sunitinib metabolism is predominantly mediated by CYP3A4 and produces an active metabolite, SU012662. This metabolite and sunitinib were the only major drug-related compounds found in the systemic circulation in mice, rats, monkeys and humans. Sunitinib and its major metabolite are highly (90-98%) protein bound in mouse, rat, monkey, and human plasma. IC_{50} values measured *in vitro* are expected to be reached with the currently recommended 50 mg dose. Sunitinib and SU012662 are not potent inducers or inhibitors of major CYP450 enzymes. Therefore, they are both predicted to have a low potential to cause clinically relevant drug-drug interactions mediated by CYP450 enzymes and efflux transporters. However, concurrent treatment with CYP3A4 inducers and inhibitors may affect sunitinib metabolism.

1.2.3.2 Clinical Experience

1.2.3.2.1 Phase 1

In an early phase 1 study designed to investigate dosing regimen and scheduling (in human subjects, the results of clinical pharmacology studies demonstrate that C_{max} and area under the concentration-time curve (AUC) increased in a proportional manner after single doses of 50 to 350 mg as well as after multiple doses of 25-100 mg), 41 patients with a variety of advanced solid tumors received sunitinib administered on a schedule of 2 weeks of treatment followed by 2 weeks off (2/2 schedule) or 4 weeks on with 2 weeks off (4/2 schedule)[84]. Doses evaluated on the 2/2 schedule (n=23) included 50 mg every other day (n=3), 50 mg daily (n=15), or 75 mg daily (n=5); the 18 patients enrolled in the 4/2 schedule received 25 mg daily (n=3) or 50 mg daily (n=15). The most frequent adverse events (AEs) were constitutional (fatigue/asthenia), gastrointestinal (nausea, vomiting, diarrhea) and hematologic (neutropenia, thrombocytopenia). Most of the AEs were grade 1 or 2, although at 75 mg daily, grade 3 and 4 fatigue/asthenia were dose limiting but readily reversible on discontinuation of treatment. There were 4 partial responses (PRs) assessed by RECIST and 22 patients with stable disease (SD) among the 41 patients.

A phase 1 dose-escalation study in 28 patients with advanced tumors evaluated sunitinib doses of 30 mg/m^2 every other day, and doses of 30, 42, or 59 mg/m^2 daily on the 4/2 schedule[85]. Grade 3 fatigue and hypertension were dose limiting at 59 mg/m^2 as well as grade 2 bullous skin toxicity, and the MTD was defined as 42 mg/m^2 daily. Based on these and other reversible AEs in the 12 patients treated at the MTD, the recommended phase 2 dose on the 4/2 schedule was determined to be 50 mg/day. Responses determined by RECIST were seen in 6 of 23 evaluable patients: 3 in RCC, 1 in NET, 1 in GIST, and 1 in adenocarcinoma of unknown primary. Tumor responses in patients treated at higher doses were often associated with reduced intratumoral vascularization and central tumor necrosis, leading to organ perforation in one patient and fistula in another. These observations suggest the possible necessity for careful tumor density monitoring to detect early evidence of necrosis.

Two phase 1 studies have been conducted in AML, the first with the primary endpoint of evaluation of the inhibition of FLT3 phosphorylation and the second designed as a conventional dose-escalation study[79, 86]. O'Farrell and colleagues[79] studied FLT3 phosphorylation in 29

AML patients who received a single dose of sunitinib at doses ranging from 50-350 mg. Over 50% of patients showed strong inhibition of Flt3 phosphorylation at doses of 200 mg and higher. As anticipated from nonclinical data, patients with FLT3 internal tandem duplication (ITD) mutations were more sensitive than those with wild-type Flt3 (FLT3-WT) as shown by 100% inhibition in FLT3-ITD compared to 50% in FLT3-WT. This study also gave evidence of downstream signal inhibition (STAT5 and ERK pathways), with STAT5 levels reduced primarily in FLT3-ITD patients while ERK inhibition occurred in the majority of patients independently of FLT3 inhibition. The dose-escalation study enrolled 15 patients with refractory or resistant AML who were treated with sunitinib on either the 4/2 or 4/1 schedule at a starting dose of 50 mg/day. Dose-limiting AEs (grade 4 fatigue and hypertension) occurred in both patients treated at 75 mg/day, and one of these patients (who had received prior mitoxantrone) developed cardiac failure. The 75-mg dose level was therefore terminated and 50 mg/day was considered to be the MTD. All four patients with FLT3 mutations had morphologic or partial responses compared to 2 of 10 evaluable patients with wild-type FLT3. Responses, although longer in patients with mutated FLT3, were of short duration.

Preliminary results from phase 1 studies exploring the combination of sunitinib with chemotherapeutic agents like capecitabine[87], pemetrexed[88], docetaxel[89], gemcitabine[90], carboplatin/paclitaxel[91], and metronomic cyclophosphamide/ methotrexate[92] in patients with various solid tumors have been presented. The MTD of sunitinib on the 4/2 schedule with docetaxel (60 mg/m$_2$) was 25 mg daily; with capecitabine (1000 mg/m$_2$), it was 37.5 mg daily. The MTD of sunitinib on the 2/1 schedule with docetaxel (75 mg/m$_2$) was 37.5 mg daily and with capecitabine (1000 mg/m$_2$) was 50 mg daily. The MTD for sunitinib as continuous daily dosing (CDD) with capecitabine (1000 mg/m$_2$) was 37.5 mg daily and for pemetrexed (500 mg/m$_2$) was 37.5 mg daily. Reported DLTs included febrile neutropenia, fatigue, hand-foot syndrome, gastrointestinal hemorrhage, cerebral hemorrhage, and ischemic optic neuropathy.

1.2.3.2.2 Phase II and Phase III in NET

A phase II trial in patients with advanced NETs who received sunitinib demonstrated a median time to tumor progression of 7.7 and 10.2 months in patients with pancreatic NETs and carcinoid tumors, respectively[63]. A follow-up randomized, double-blind phase III trial comparing the response of 86 randomly selected patients given sunitinib with that of 85 patients on placebo demonstrated significant improvement in median PFS of patients on sunitinib (11.4 months versus 5.5 months)[53]. Moreover, patients treated with sunitinib showed early signs of an increase in overall survival[54]. Based on these findings sunitinib was approved by the FDA for the treatment of progressive, unresectable, locally advanced or metastatic PNETs. Unfortunately, none of these clinical trials evaluated what pathways or genes were altered in patient tumor samples and whether response to sunitinib was related to the tumor genotype.

1.2.3.3 Safety Profile

Sunitinib is reasonably well tolerated, with asthenia, hypertension, dermatitis, and mild myelosuppression as the most common AEs.[93] Additionally, the inhibition of TKRs by agents such as sunitinib can result in cutaneous AEs such as acral erythema, subungual splinter hemorrhages, modification of hair and skin pigmentation, mucositis, and (occasionally) periocular edema[94, 95]. Hand-foot skin reaction, a group of signs and symptoms that can affect, usually bilaterally, the hands and/or feet of patients, has occurred in patients receiving sunitinib. A recent analysis of dermatological AEs in patients receiving sunitinib therapy has

reported that all-grade hand-foot skin reactions occurred in 19% of patients (5% grades 3-4), skin discoloration in 28% (no grades 3-4), dry skin in 16% (1% grades 3-4), skin rash in 13% (1% grades 3-4), dermatitis in 8% (2% grades 3-4), hair color changes in 10% (no grades 3-4), alopecia in 6% (no grades 3-4), and phototoxicity in <0.1% (no grades 3-4)[96].

1.2.4 Rationale

The approval, by the FDA, of sunitinib and everolimus for the treatment of unresectable, locally advanced or metastatic NETs is a remarkable milestone in the field of medical therapy of malignant NETs[53-55]. However, there is important management issue that need to be addressed: While the choice of targeted therapies in other malignancies is driven by the findings of the precise molecular alterations present in the tumor, no such study has been done in malignant NETs. This is particularly important given that the survival of patients with malignant NETs appears to be different based on the driver mutation(s) present in the tumor and low- or intermediate grade tumors can have a relatively indolent growth[58].

Surgical resection alone is a valuable treatment option for patients with early-stage disease; however, the extent, timing and effect of surgical intervention for advanced, metastatic NETs remain controversial and difficult to estimate. NETs most commonly metastasize to the loco-regional lymph nodes and liver and 25% to 93% of patients will develop liver metastases throughout the course of their disease[38, 43]. Prospective randomized data on the treatment of liver metastases of NETs are lacking and there is also considerable debate regarding the optimal surgical management[42]. In general, the surgical strategies proposed by different groups can be classified into: 1) resection of the primary tumor and loco-regional metastases (intra-abdominal debulking), 2) resection of isolated liver metastases, or 3) synchronous resection of primary and liver metastases.

Although not supported by randomized clinical trial data, currently it is advocated that surgery should be undertaken only if metastatic disease is confined to the liver and if 90% or more of the tumor mass, including liver metastases, can be successfully removed[47]. However, most patients will present with multiple bilobar liver metastases, and altogether only 5–10% will have apparently solitary or dominant liver metastases amenable to surgical resection[43, 97]. Furthermore, recurrence after surgery is common and a significant number of patients with advanced NETs undergoing debulking surgery will have residual disease and suffer from complications associated with hormonal hypersecretion and or tumor progression[43, 48, 49]. The role of surgical tumor debulking less than the traditionally accepted 90% of tumor mass is currently unknown and it is not clear if adjuvant therapy in this patient population will render favorable outcomes.

Although improving OS is the ultimate goal for any cancer therapy, the variable, and at times long, survival time in many patients with NETs makes OS a less suitable initial end point to study for the proposed strategy of targeted therapy [49, 71]. In this regard, using PFS as a primary end point poses less significant scientific challenges and is attractive from both an ethical and feasibility standpoint[49]. Such an approach will allow us to generate enough data to determine whether a larger study is warranted using genotype targeted therapy.

2 Eligibility assessment and enrollment

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Progressive, histologically or cytologically diagnosed low or intermediate grade, neuroendocrine tumors confirmed by the Laboratory of Pathology, NCI or a pathology laboratory at the enrolling institution. Disease progression is defined according to RECIST criteria for progression of disease (see Section **6.3**) or any new lesions seen on 68-Gallium DOTATATE within 18 months prior to enrolment (per PI discretion and if 68-Gallium DOTATATE is performed at the enrolling institution).

2.1.1.2 Age ≥ 18 years, because the incidence and prevalence of metastatic pancreatic and gastrointestinal neuroendocrine tumors in the pediatric patient population is exceedingly rare (children are excluded from this study, but will be eligible for future pediatric trials).

2.1.1.3 Patients must have measurable disease according to RECIST criteria (see Section **6.3**) on anatomic imaging studies (CT scan or MRI).

2.1.1.4 Willingness to undergo tumor biopsy if the patient does not have a known familial cancer syndrome (MEN1, VHL and NF1) or archival tissue available.

2.1.1.5 ECOG performance status <2 (see **Appendices**

2.1.1.6 **Appendix** A).

2.1.1.7 Patients must have normal organ and bone marrow function as defined below:

- hemoglobin	≥ 9 g/dL*
- leukocytes	≥3,000/mcL*
- absolute neutrophil count	≥1,500/mcL*
- platelets	≥ institutional lower limit of normal*
- total bilirubin	within normal institutional limits
- AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal (≤5 x ULN in patients with liver metastases)
- creatinine	within normal institutional limits
	OR
- creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.
- INR	≤2;

*If a patient's bone marrow function falls below the indicated values and it is not thought to be related to prior treatments a hematology consult will be ordered. If Hematology deems the patients safe to proceed with treatment they will be allowed to enroll on study. In such cases, the patient's absolute neutrophil count must be > 1,000/mcl, hemoglobin must be > 7.5 g/dL and the platelet count must be > 75,000 mcL. Each patient will also be seen by a medical oncologist at follow-up visits if possible.

2.1.1.8 Fasting serum cholesterol ≤300 mg/dL OR ≤7.75 mmol/L AND fasting triglycerides ≤2.5x ULN. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication;

2.1.1.9 Women of childbearing potential (WOCBP) or partners of WOCBP participating in this study must agree to use highly effective contraception while on treatment and for at least 8 weeks after end of treatment, because the effects of sunitinib and everolimus on the developing human fetus are unknown. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

Highly effective contraception methods include combination of:

a. Any two of the following:
   - Use of oral, injected or implanted hormonal methods of contraception or;
   - Placement of an intrauterine device (IUD) or intrauterine system (IUS);
   - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository;

b. Total abstinence or;

c. Male/female sterilization.

Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to enrollment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.

2.1.1.10 Must have fully recovered from toxicities of any prior treatment with cytotoxic drugs, radiotherapy, surgery, or other anti-cancer modalities (returned to baseline status as noted before most recent treatment or ≤ grade 1).

2.1.1.11 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.2 Exclusion Criteria

2.1.2.1 Uncontrolled hypertension (>150/100 mmHg).

2.1.2.2 Prior external beam radiation therapy to the target lesion(s) within 1 months prior to enrollment

2.1.2.3 Prior systemic chemotherapy or therapy with one of the investigational agents within 1 month prior to enrollment.

2.1.2.4 Patients who had therapy with one of the investigational agents more than 1 month prior to enrollment in whom tumor genotyping show assignment to the same investigational agent.

2.1.2.5 Patients who are receiving any other investigational agents.

2.1.2.6 Patients with known brain metastases will be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

2.1.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to sunitinib or everolimus.

2.1.2.8 Patients who have any severe and/or uncontrolled medical conditions such as:

a. unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤6 months prior to start of everolimus, serious uncontrolled cardiac arrhythmia, or any other clinically significant cardiac disease
b. symptomatic congestive heart failure of New York heart Association Class III or IV
c. active (acute or chronic) or uncontrolled severe infection, liver disease such as cirrhosis, decompensated liver disease
d. known severely impaired lung function
e. QTc interval > 450 msec for males or > 470 msec for females
f. active, bleeding diathesis;
g. psychiatric illness/social situations that would preclude informed consent, limit compliance with study requirements

2.1.2.9 Pregnant or nursing patients will be excluded from the study, because the effects of sunitinib and everolimus on the developing human fetus are unknown. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with sunitinib or everolimus, breastfeeding should be discontinued if the mother is treated with sunitinib or everolimus (**See also Appendix B**).

2.1.2.10 Current treatment with therapeutic doses of Coumadin-derivative anticoagulants (low dose Coumadin up to 2 mg PO daily for deep vein thrombosis prophylaxis is allowed).

2.1.2.11 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with study agents.

2.1.2.12 Lack of physical integrity of the upper gastrointestinal tract or malabsorption syndrome, or the inability to take oral medication

2.1.2.13 Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy. Patients with a known history or diagnosis of diabetes mellitus who are on therapy and have had good blood sugar control may be included even if the HbA1c is > 8% because this value can take up to 3-4 months to normalize;

2.1.2.14 Patients who have received live attenuated vaccines within 1 week of start of everolimus and during the study. Patient should also avoid close contact with others who have received live attenuated vaccines. Examples of live attenuated vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines

2.1.2.15 Patients who are on chronic treatment with corticosteroids or other immunosuppressive agents (topical or inhaled corticosteroids are allowed)

2.1.2.16 Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study

2.1.2.17 Patients who are taking medications that are strong inhibitors of CYP3A4 or PgP and need to remain on these medications. For a current table of Substrates, Inhibitors and Inducers please access the following

website:http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

2.1.2.18 Patients who have a history of another primary malignancy from which the patient has been disease free for < 3 years at the time of enrolment, with the exceptions of: a patient with a familial cancer syndrome-associated NETs including MEN1, VHL, NF-1, and TS

2.2 SCREENING EVALUATION

Within 4 weeks prior to enrollment

- Confirmation of progressive, histologically or cytologically diagnosed low or intermediate grade, neuroendocrine tumors locally invasive or metastatic confirmed by the Laboratory of Pathology and the Department of Radiology, NCI or a pathology laboratory and radiology department at the enrolling institution (any time prior to enrollment).
- Brain MRI or CT (if clinically indicated)
- 68-Gallium DOTATATE scan per PI discretion
- Contrast enhanced CT scan or MRI of the chest, abdomen and pelvis (CT C/A/P)
- Bone scan for patients in whom bone metastases are suspected
- FDG PET scan
- HIV antibody
- 24-urine collection and measurement of urinary creatinine, total protein and albumin, and serum creatinine measurement

Within 2 weeks prior to enrollment

- Laboratory Evaluations
    - CBC with differential and platelets
    - Chemistries: Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Total Protein
    - INR
    - Lipid panel (fasting)
    - Hemoglobin A1C
- Complete history and physical examination including height, weight, vital signs and ECOG status
- 12 lead ECG

Within 3 days prior to enrollment

- Serum or urine beta-HCG (in women of childbearing potential)

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.3.1 Treatment Assignment Procedures (**For registration purposes only**):

Cohorts

Number	Name	Description
1	Cohort 1	Subjects with wild type NETs or mutations in MEN1/PDGFR/KIT/FLT3 or mutations not known to be specifically targeted by sunitinib or everolimus
2	Cohort 2	Subjects with NETs and mutations in NF1/PTEN/PI3K/AKT/mTOR/VH/TP53L but not in MEN1/PDGFR/KIT/FLT3

Arms

Number	Name	Description
1	Arm 1	Sunitinib
2	Arm 2	Everolimus

Arms Assignments

Subjects in Cohorts 1 will be directly assigned to Arm 1.

Subjects in Cohorts 2 will be directly assigned to Arm 2.

Subjects who develop disease progression or unacceptable treatment-related toxicity during treatment in either Arm 1 or Arm 2 will cross-over to the other Arm.

2.4 BASELINE EVALUATION

Studies do not need to be repeated if they have already been performed for screening within the required baseline timeframe.

Within 4 weeks prior to study drug initiation

- Echocardiogram in patients with Carcinoid tumors.
- Patients must provide archival tissue or undergo image guided tumor biopsy for genotyping (patients with known familial cancer syndrome (MEN1, VHL and NF1) are excluded)

- Patients who present with evidence of cardiac or pulmonary risk factors will undergo a cardiac evaluation prior to biopsy/surgical intervention according to standard clinical practice
- 30 mL of peripheral blood for research
- 2-13 mL saliva for research studies
- Hepatitis B and C serology and viral load (if positive serology)

Within 2 weeks prior to study drug initiation

- Laboratory Evaluations
  - Chromogranin A.
  - Only in patients known to have functioning NETs or with a prior history of elevation of secreting biomarkers: vasoactive intestinal polypeptide (VIP), serotonin (urinary 5-HIAA), gastrin, somatostatin, fasting insulin, C-peptide (proinsulin) or glucagon.
- CT C/A/P or MRI

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

In this Phase II trial, patients first will undergo tumor genotyping from their archival tumor tissue samples. Patients who do not have archival tumor tissue samples available, will have image guided tumor biopsy. Patients with VHL and MEN1 will not undergo tumor biopsy.

Based on the tumor genotype or germline mutation status, patients will be treated with sunitinib (Arm 1) (for mutations in *MEN1/PDGFR/KIT/FLT3*) or everolimus (Arm 2) (for mutations in *NF1/PTEN/PI3K/AKT/mTOR/VH/TP53L*) daily in 28 day cycles (**Figure 2, Table 3**). Patients will receive long-acting octreotide (for symptoms associated with hormonal hypersecretion). Patients who have gene mutations not known to be specifically targeted by sunitinib or everolimus or with more than one mutation will be assigned to sunitinib (Arm 1) (**Table 3, Appendix C** and **Appendix D**).

If a patient has two mutations (one in the sunitinib-*MEN1/PDGFR/KIT/FLT3* and another in the everolimus group- *NF1/PTEN/PI3K/AKT/mTOR/VHL/TP53*, the patient will be assigned to sunitinib (Arm 1).

3.1.1 Cross-over

Patients who develop disease-progression or unacceptable treatment-related toxicity on either sunitinib or everolimus will cross-over to the other drug.

Patients must start cross-over within 3 months of discontinuation of the first line of treatment. Unacceptable toxicity must have resolved to CTCAE Grade 1 or baseline.

Before cross-over eligibility must be confirmed (tests do not need to be repeated if they have already been performed within the required timeframe):

Within 4 weeks prior:

- CT C/A/P or MRI

Within 2 weeks prior:

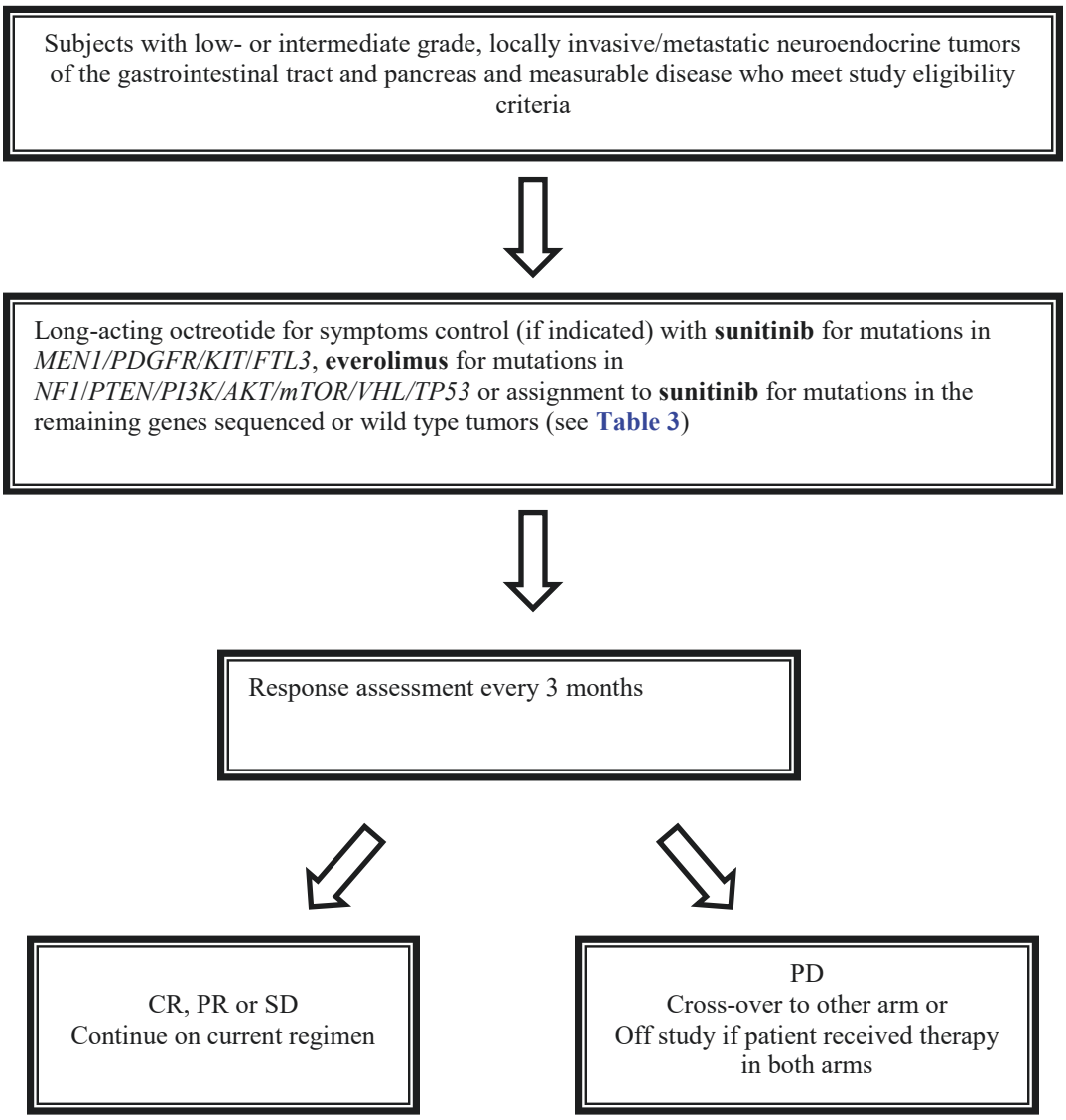
- Physical examination including weight, vital signs and ECOG status
- Laboratory Evaluations
    - CBC with differential and platelets
    - Chemistries: Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Total Protein

During cross-over treatment patients will have regular study assessments as described in Study Calendar Error! Reference source not found.

3.1.2 Long term follow up

After discontinuation from the study, the subjects will be contacted at 3 months intervals to obtain information about subsequent treatment(s) and survival status by phone or e-mail.

Figure 2. Study flow chart and treatment selection based on tumor genotype.



CR-complete response, PR-partial response, SD-stable disease, PD-disease progression

Treatment will continue until disease progression, unacceptable treatment-related toxicity, or consent withdrawal. Response to treatment (CR/PR/SD) will be assessed using RECIST v1.1 (See Section **6.3**) every 3 months after initiation of treatment.

3.2 STUDY DRUG ADMINISTRATION

3.2.1 Sunitinib Treatment and dose

Patients on Arm 1 will be treated with oral sunitinib at a starting dose of 37.5 mg once daily.

Patients will take sunitinib once daily in the morning, with or without food, as desired. Patients should be advised to drink plenty of water or take rehydration fluids to avoid dehydration if

diarrhea occurs. If a dose is missed the subject will be instructed to take the next dose as scheduled.

3.2.1.1 Because hypertension is a known and potentially serious adverse event associated with sunitinib maleate treatment, patients will have their blood pressure monitored and recorded at baseline and weekly during sunitinib treatment either at the doctor's office or using any calibrated electronic device (such as those found at a local drug store or pharmacy). **Appendix E** detail the collection and recording of blood pressure related information.

3.2.1.2 Patients with bulky solid tumors should be monitored closely for pneumothorax, intestinal fistulae, or intestinal perforation in the event of rapid tumor destruction.

3.2.1.3 Patients should be alerted to the possibility that sunitinib capsules can cause a yellow discoloration of the skin on direct contact. If this happens, the patient should wash immediately with soap and water.

3.2.1.4 Thyroid function (free T4, T3 and TSH) will be monitored at every cycle).

3.2.2 Everolimus Treatment and dose

Patients on Arm 2 will be treated with oral everolimus at a starting dose of 10 mg once daily.

The tablets should be swallowed whole with a glass of water and should not be chewed or crushed. For patients unable to swallow tablets, the tablet(s) should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring until the tablet(s) is fully disintegrated (approximately 7 minutes), immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse completely swallowed to ensure the entire dose is administered.

If vomiting occurs, no attempt should be made to replace the vomited dose. Patients should be instructed that if they miss a dose on one day, they must not take any extra dose the next day, but instead to immediately contact the study center as soon as possible to ask for advice.

Table 3. Choice of targeted therapy driven by the findings of the precise molecular alterations based on common mutations that occur in NETs.

Study Agent	Mutations *	Affected Pathways	
Everolimus	*PTEN*	*PI3K/AKT/mTOR*	
	PI3K	*PI3K/AKT/mTOR*	
	AKT	*PI3K/AKT/mTOR*	
	mTOR	*PI3K/AKT/mTOR*	
	VHL	Hypoxia induced *PI3K/AKT/mTOR*	
	TSC1	*PI3K/AKT/mTOR*	
	TSC2	*PI3K/AKT/mTOR*	
	NF1	*TSC2/mTOR,* Hypoxia induced neoangiogenesis	
Sunitinib	*MEN1*	Cell growth, cell cycle and genome instability	
	FLT3	Cell survival, proliferation, and differentiation	
	PDGFR	Cell proliferation, cell migration, neoangiogenesis	
	ATM		
	KIT	Cell survival, proliferation, and differentiation	
	ATRX	Cell survival, proliferation, and differentiation	

*Mutations in genes not listed above or that are wildtype will be treated with sunitinib (see **Appendix C** for list of other genes that will be genotyped). Germline DNA will be obtained for comparison to tumor genotype data for every patient. Also, some patients with known familial cancer syndromes (MEN1 and VHL) will be included in the study and tumor biopsy for the sole purpose of agent selection in these patients will not be performed.

3.2.3 CCR Self-Administered Study Drugs Policy

All oral self-administered investigational agents will be properly accounted for, handled, and disposed in accordance with existing federal regulations and principles of Good Clinical Practice. All oral study drugs will be recorded in the patient diary found in **Appendix F**. This will be used as a memory aide for subjects. The clinical research team will maintain the primary source record.

Subjects should be asked to bring the diary as well as unused study agent and empty containers with them at each study visit. If a subject goes off study while at home, the research nurse will ensure and document the return of the unused oral investigational agents from the participant.

Unused investigational study agents will be disposed and destroyed per CC pharmacy SOPs.

3.3 DOSE MODIFICATIONS/DOSE DELAY

Patients are allowed to remain off treatment for up to 12 weeks.
Patients requiring >12 weeks of study medication dose interruption due to persistent toxicity will be either crossed over to the other arm or discontinued from the treatment.

3.3.1 Sunitinib

Subjects experiencing severe toxicity (see dose modification **Table 5** below) will have 1-week treatment rests inserted into the regimen as needed and may dose reduce depending on individual

tolerability. The dose of 37.5 mg may be reduced to 25 mg daily, which is the minimum dose acceptable for daily dosing of sunitinib. Intra-patient re-escalation of study medication back to previous dose is permitted at the discretion of the investigator and considering the patient's clinical status.

Subjects not experiencing a response by RECIST criteria and experiencing only Grade ≤1 non-hematological or Grade ≤2 hematological toxicity within the first 8 weeks of treatment may dose escalate to 50 mg daily at any time after 8 weeks. If dose is escalated or reduced, treatment will continue to be on a continuous daily dosing schedule.

The doses of study medication may be modified as outlined in **Table 4**.

Table 4: Sunitinib Dose levels

Dose Level	Daily Dose	Dispensed As
-1	25 mg*	1 x 25 mg capsule or 2 x 12.5 mg capsule
0 (Starting Dose Level)	37.5 mg	3 x 12.5 mg capsule
+1	50 mg	1 x 50 mg capsule or 2 x 25 mg capsules)
*Patients will not be treated at less than 25 mg per day. If a dose reduction is required at this level, the subject will be removed from study therapy		

Intrapatient dose reduction by 1 dose level (to 25 mg/day, or to 37.5 mg/day if the subject has been receiving 50 mg/day) may be required depending on the type and severity of toxicity encountered. In **Table 5** is an outline of the recommended dose modifications for study treatment-associated toxicity that will be used in this protocol.

Table 5. Dose Modifications for Sunitinib - Associated Toxicity

Toxicity	Grade 1/2[1]	Grade 3	Grade 4
Hypertension	See **Table 6**	See **Table 6**	See **Table 6**
Other Non-hematologic	Continue at the same dose level.	• Withhold dose until toxicity is Grade ≤1 or has returned to baseline, then resume treatment at the same dose level. • If the toxicity recurs with Grade 3 severity (except hepatotoxicity), at the discretion of the investigator, reduce the dose by 1 level. • If ASL/ALT or bilirubin elevation recurs with grade 3 severity, the patient will be removed from the study.	Withhold dose until toxicity is Grade ≤1 or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator

Toxicity	Grade 1/2[1]	Grade 3	Grade 4
Hematologic	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤2 or has returned to baseline, then resume treatment at the same dose level[2]. If the toxicity recurs with Grade 3 severity, at the discretion of the investigator, reduce the dose by 1 level	Withhold dose until toxicity is Grade ≤2 or has returned to baseline, then reduce the dose by 1 level and resume treatment[2]
[1]If after the first 8 weeks there is no response according to RECIST and toxicity remains ≤ non-hematological Grade 1 or ≤ hematological Grade 2 dose escalation to 50 mg/day may be considered. [2] Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting, or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption. Complicated neutropenia includes duration of Grade 4 longer than 7 days or concurrent fever or infection.			

3.3.1.1 Dose Modification for Sunitinib related hypertension

Increases in blood pressure (BP) and cases of hypertension have been associated with many drugs acting on the VEGF pathway. The proposed mechanism for this increase is through inhibition of VEGF-induced peripheral vasodilation. Hypertension following sunitinib treatment has rarely been seen in animal studies or clinical trials. Dose modification guidelines are provided below and will be used in this protocol. Please see Section **4.1.1** for medical management guidelines.

Table 6 Recommended Dose Modification Hypertension Monitoring and Management

Grade (CTCAE v4)	**Antihypertensive Therapy**	**Blood Pressure Monitoring**	**Sunitinib Dose Modification**
Persistent Grade 1 Pre-hypertension Systolic 120-139 Diastolic 80-90		Standard	No change
Persistent Grade 2-Moderate Systolic 140-159 Diastolic 90-99 Protocol-specific guidance supersedes any other management guidelines, including	Step 1) Initiate LA DHP CCB treatment and if needed, after 24-48 hr. Rx, increase dose in stepwise fashion every 24-48 hours until BP is controlled or at max dose of Rx Step 2) If BP still not controlled, add another	BP should be monitored as recommended by the treating physician	No change except as described in step 4

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Sunitinib Dose Modification
CTCAE v4	antihypertensive Rx, a BB, ACE1, ARB, or ABB; increase dose of this drug as described in step 1 Step 3) If BP still not controlled, add 3rd drug from the list of antihypertensives in step 2; increase dose of this drug as described in step 1 Step 4) If BP still not controlled, consider either 1 dose reduction of sunitinib or stopping sunitinib *NOTE: Stopping or reducing the dose of sunitinib is expected to cause a decrease in BP the treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly.*		

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Sunitinib Dose Modification
Persistent Grade 3 Severe Systolic ≥160 Diastolic ≥100 Protocol-specific guidance supersedes any other management guidelines, including CTCAE v4	HOLD sunitinib until systolic BP ≤159 and diastolic BP ≤99. BP management is identical to that for Grade 2 (see steps 1-4 above) **with 2 major exceptions:** **1) If systolic BP >180 or diastolic BP >110 and the patient is symptomatic: optimal management with intensive IV support in ICU; STOP sunitinib and notify hospital staff that stopping sunitinib may result in a decrease in BP** **and** **2) If systolic BP >180 or diastolic BP >110 and the patient is asymptomatic, 2 new anti-hypertensives must be given together in step 1 (and dose escalated appropriately as in step 1).** *NOTE: Stopping or reducing the dose of sunitinib is expected to cause a decrease in BP the treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly*	BP should be monitored as recommended by the treating physician **unless the patient is symptomatic with systolic BP >180 or diastolic BP >110 in which case, monitoring should be intensive.**	HOLD sunitinib until systolic BP ≤159 and diastolic BP ≤99. In most circumstances, if BP cannot be controlled after an optimal trial of anti-hypertensive medications, consider either 1 dose reduction of sunitinib or stopping sunitinib. **HOWEVER, if the patient requires hospitalization for management of symptomatic systolic BP >180 or diastolic BP >110,** permanently discontinue sunitinib or if BP is controlled, re-start sunitinib at 1 lower dose level after consultation with the study Principal Investigator
Grade 4 Life-threatening consequences of hypertension	**Optimal management with intensive IV support in ICU; STOP sunitinib and notify hospital staff that stopping sunitinib may result in a decrease in BP**	Intensive	Permanently discontinue sunitinib or if BP is controlled, re-start sunitinib at 1 lower dose level after consultation with the study

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Sunitinib Dose Modification
			Principal Investigator

Abbreviations: dihydropyridine calcium-channel blockers (DHP-CCB), selective beta blockers (BB), angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), alpha beta blocker (ABB)

- *See table below for suggested antihypertensive medications by class
- If patients require a delay of >2 weeks for management of hypertension, discontinue protocol therapy
- If patients require >2 dose reductions, discontinue protocol therapy
- Patients may have up to 2 drugs for management of hypertension prior to any dose reduction in sunitinib
- 24-48 hours should elapse between modifications of anti-hypertensive therapy
- Hypertension should be graded using CTCAE v4.

3.3.2 Everolimus

3.3.2.1 Hepatic impairment dose modifications

Please see **Appendix G** for determination of Child-Pugh classifications.

- Mild hepatic impairment (Child-Pugh A) – the recommended starting dose is 7.5 mg daily.
- Moderate hepatic impairment (Child-Pugh B) – the recommended starting dose is 5 mg daily.
- Severe hepatic impairment (Child-Pugh C) – not recommended. If the desired benefit outweighs the risk, a dose of 2.5 mg daily must not be exceeded.
- Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment.

3.3.2.2 Dose delay

Everolimus treatment will be discontinued if a dose interruption exceeds 4 weeks (28 days).

3.3.2.3 Dosing modifications

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. Details of study treatment schedule adjustments and dose levels are provided in **Table 7**

Table 7: Everolimus Dose Levels

Dose Level	Daily Dose	Dispensed As
0 – Starting dose level for patients without hepatic impairment*.	10 mg	1 x 10 mg tablets or 2 x 5 mg tablets or 4 x 2.5 mg tablets
-1	5 mg	1 x 5 mg tablets or

		2 x 2.5 mg tablets
-2	5 mg every other day‡	1 x 5 mg tablets or 2 x 2.5 mg tablets
*See Section **3.3.2.1** for definition and starting doses for hepatic impairment. ‡ Patients requiring dose reduction below this level will be removed from the study therapy		

If treatment is interrupted due to toxicity, everolimus should not be resumed until recovery to grade ≤1, then reintroduce everolimus at the initial dose or lower dose level depending on toxicity type and Grade.

If a patient has already decreased 2 dose levels, no further dose reduction is permitted. Patients requiring a third dose reduction will be required to discontinue study treatment. The following Table provides the procedure to be followed for dose modification and re-initiation of everolimus in the event of toxicities suspected to be related to the study drug.

Table 8 and **Table 9** list the dosing guidelines for everolimus-related non-hematologic and hematologic toxicities.

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption (with or without dose reduction) of everolimus therapy.

The following sections summarize recommendations for dose interruption, reduction, or discontinuation of everolimus in the management of ADRs. General management recommendations are also provided as applicable. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Table 8: Dosing guidelines for everolimus-related non-hematologic toxicities

Toxicity	Action
Non-Infectious Pneumonitis	Please refer to **4.1.2.9**
Reactivation of HBV or HCV flare	Please refer to **4.1.2.10**
AST or ALT elevation Grade 1 (> ULN - 3.0 x ULN) Grade 2 (> 3.0 - 5.0 x ULN)	Maintain current dose level
AST or ALT elevation Grade 3 (> 5.0 - 20.0 ULN)*	Interrupt everolimus administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs within ≤ 7 days, everolimus should be re-started at the dose level prior to interruption. If resolution takes > 7 days, or if event reoccurs within 28 days, hold everolimus until recovery to ≤ grade 1 or baseline grade / value and reintroduce everolimus at one dose level lower. .
AST or ALT elevation Grade 4 (> 20 x ULN)*	Interrupt everolimus administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs within ≤ 7 days, everolimus should be re-started at one dose level lower. If resolution takes > 7 days, discontinue everolimus.

Toxicity	Action
Intolerable grade 2 mucositis, or grade 3 AE, except hyperglycemia or hypertriglyceridemia or hypercholesterolemia (see Section **4.1.2.6**)	Interrupt everolimus administration until resolution to ≤ grade 1 or baseline grade / value. If resolution occurs within ≤ 7 days, everolimus should be re-started at the dose level prior to interruption. If resolution takes > 7 days, or if event reoccurs within 28 days, hold everolimus until recovery to ≤ grade 1 or baseline grade / value and reintroduce everolimus at one dose level lower.
Any other grade 4	Hold everolimus until recovery to grade ≤ 1 or baseline value Reintroduce everolimus at one dose level lower, if available.
Grade 3 or 4 clinical liver failure (asterixis or encephalopathy/coma)	Discontinue everolimus
Recurrence of intolerable grade 2 mucositis or grade 3 event after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is 2.5 mg daily. Below this level, everolimus must be discontinued. If toxicity recurs at Grade 3, consider discontinuation
Recurrence of grade 4 after dose reduction	Discontinue everolimus
Any non-hematologic toxicity requiring everolimus interruption for > 28 days	Discontinue everolimus
* Should HCV flare be confirmed, the guidelines for flare must take precedence (**4.1.2.10**)	

Table 9 Dosing guidelines for Everolimus-related hematologic toxicities

Toxicity	Action
Grade 2 thrombocytopenia (platelets <75, ≥ 50x109/L)	No action
Grade 3 thrombocytopenia (platelets <50, ≥ 25 x109/L)	Interrupt everolimus until resolution to grade ≤1 If resolution occurs within ≤ 7 days, reintroduce everolimus at the dose level prior to interruption. If resolution occurs after more than 7 days, or event reoccurs within 28 days, reintroduce everolimus at one dose level lower.
Grade 4 thrombocytopenia (platelets < 25 x109/L)	Interrupt everolimus until recovery to grade ≤ 1. Then reintroduce everolimus at one dose level lower.
Grade 3 neutropenia or anemia (neutrophil <1, ≥0.5 x109/L)	Interrupt everolimus until resolution to grade ≤1 or baseline value If AE resolution occurs ≤ 7 days, reintroduce everolimus at the same dose level. If AE resolution occurs > 7 days, or event reoccurs within 28 days, reintroduce everolimus at one dose level lower.
Grade 4 neutropenia or anemia	Interrupt everolimus until recovery to grade ≤ 1 or baseline value. Reintroduce everolimus at one dose level lower.*
Febrile neutropenia	Interrupt everolimus until resolution to grade ≤ 1 (or baseline value) and no fever. Reintroduce everolimus at one dose level lower.*
Recurrence of grade 3 toxicity after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is 5 mg every other day (2.5 mg daily). Below this level, everolimus must be discontinued
***Recurrence of grade 4 toxicity (including febrile neutropenia) after dose reduction**	**Discontinue everolimus**
***Any hematologic toxicity requiring everolimus interruption for > 28 days**	**Discontinue everolimus**

3.4 STUDY CALENDAR

Cycle is 28 days. A time window of up to 7 days before or after the scheduled visit day will be permitted in order to accommodate weekends, holidays, travel delays, inclement weather and other such unexpected events.

Screening for eligibility	
Within 4 weeks prior to enrollment	• 24-hour urine collection for urine protein, urine creatinine and urine albumin • HIV antibody • Radiological evaluations[1] • Histopathological confirmation of neuroendocrine tumors
Within 2 weeks prior to enrollment	• Hemoglobin A1C • 12- lead ECG • CBC, Chemistries[2], INR, Lipid panel (fasting) • Clinical Assessments[3]
Within 3 days prior to enrollment	• Serum or urine HCG (in women of childbearing potential only)
Enrollment	
• Patient signs consent • Advance Directive [4]	
Baseline Tests need not be repeated if they have been done during the appropriate timeframe at screening	
Within 4 weeks prior to treatment initiation	• Hepatitis B and C Evaluation • Echocardiogram (in patients with carcinoid tumors only) • Image guided tumor biopsy for genotyping (patients with known familial cancer syndrome (MEN1, VHL and NF1) and with available archival tissue are excluded) • Cardiac Evaluation (in patients that present with cardiac or pulmonary risk factors) • 30 mL of peripheral blood for research • 2-13 mL saliva for research studies
Within 2 weeks prior to treatment initiation	• Chromogranin A • VIP, urinary 5-HIAA, gastrin, somatostatin, fasting insulin, C-peptide (proinsulin) and or glucagon only in patients known to have functioning NETs or with a prior history of elevation of secreting biomarkers.

		• CT C/A/P or MRI
Treatment cycles based on tumor genotyping (1 cycle=28 days)		
Cycle 1	**Day 1** within 2 weeks prior to treatment	• Clinical Assessment[3] • CBC, Chemistries[2], free T4, T3, TSH • Urinalysis • 12 lead ECG • Concomitant Medications • Adverse Events • Urine or serum HCG in women of childbearing potential (within 3 days before treatment)
	Day 15 within 1 week prior to treatment	• Clinical assessment[3] • CBC and Chemistries[2] • Urinalysis • Concomitant Medications • Adverse Events
Cycle 2	**Day 1** within 1 week prior to treatment or cross-over treatment	• Clinical assessment[3] • CBC, Chemistries[2], free T4, T3, TSH • Urinalysis • 12 lead ECG • Concomitant Medications • Adverse Events • Urine or serum HCG in women of childbearing potential (within 3 days before study drug initiation)
	Day 15 within 1 week prior to treatment	• CBC, • Chemistries, • Urinalysis • Concomitant Medications • Adverse Events
Cycle N	**Day 1** within 1 week prior to treatment or cross-over treatment	• Clinical assessment[3] • CBC, Chemistries[2], free T4, T3, TSH • Chromogranin A (every 3 months) • Urinalysis • 12 lead ECG • Concomitant Medications • Adverse Events • Radiological evaluation of treatment response[5] • Urine or serum HCG in women of childbearing

		potential (within 3 days before study drug initiation)
Safety Follow Up Visit (approximately 30 days after last dose of study drug)		
• Clinical assessment[3] • CBC, Chemistries[2], free T4, T3, TSH • Urine or serum HCG in women of childbearing potential • Urinalysis • Radiological evaluation of treatment response[5] (not applicable for patients that have progressed on 2 drugs) • Concomitant Medications • Adverse Events		
Long Term Follow up		
Telephone contact or e-mail every 3 months to determine anti-cancer therapy and survival status		

[1] Radiological Evaluations to be completed as part of the screening.

- Brain MRI or CT (if clinically indicated)
- 68-Gallium DOTATATE scan per PI discretion
- Contrast CT scan or MRI of the chest, abdomen and pelvis (CT C/A/P)
- Bone scan for patients in whom bone metastases are suspected
- FDG PET scan

[2] Chemistries: Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Total Protein

[3] Clinical assessments: Complete history (screening only) and physical examination including height (screening only), weight, vital signs and ECOG

[4] Filling out of the advanced directives will be offered, but obtaining of it is not required. For details see Section **10.3**

[5] A CT or MRI of the chest/abdomen/pelvis to reassess treatment response will be done every 3 months after treatment initiation

3.5 Criteria for Removal from Protocol Therapy and Off Study Criteria

3.5.1 Criteria for removal from protocol therapy

The criteria that take the subject off active protocol therapy include:

- Progressive disease on each study arm
- Participant requests to be withdrawn from active therapy
- Unacceptable Toxicity as defined in Section **3.3**
- Investigator discretion
- Positive pregnancy test

In all cases, a safety follow up visit will be conducted within approximately 30 days of the last dose of study drug therapy.

3.5.2 Off-Study Criteria

The criteria that take the subject off study include:

- Participant requests to be withdrawn from study*
- Patient lost to follow up
- Investigator discretion
- Screen failure
- Death
- PI decision to close the study

* If patient is still on active therapy at the time of request, patients will be encouraged to undergo a follow up safety visit approximately 30 days from the last dose of study drug prior to being removed from the study.

3.5.3 Off Protocol Therapy and Off Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the website (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 SUPPORTIVE CARE

- Long-acting octreotide (Sandostatin® LAR Depot) is a somatostatin analogue which has been used in combination with everolimus or sunitinib for symptoms control[49, 57]. Common side effects of long-acting octreotide include gallstones (24%), hyperglycemia (27%) and hypoglycemia (4%). Octreotide will be only administered to patients with carcinoid syndrome for symptom control and patients already on it will be continued on the medication.
- Long-acting octreotide will be administered at a dose of 30 mg intramuscularly every 28 days for control of carcinoid symptoms or at the dose the patient is already on at enrollment.
- Standard medical therapy will be utilized in the management of everolimus and sunitinib toxicity. The sections provide recommendations for management of specific toxicities.

4.1.1 Management of Sunitinib-Induced Hypertension

Table 10 Oral Antihypertensive Medications

Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug-interactions with sunitinib through CYP450.

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Dihydro-pyridine Calcium-Channel Blockers (DHP CCB)	**nifedipine XL**	**30 mg daily**	**60 mg daily**	**90 mg daily**	**CYP 3A4 substrate**
	amlodipine	**2.5 mg daily**	**5 mg daily**	**10 mg daily**	**CYP 3A4 substrate**
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate and inhibitor
Selective β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	atenolol	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	Yes (CYP450 unknown)
Angiotensin Converting Enzyme Inhibitors (ACEIs)	captopril	12.5 mg 3x daily	25 mg 3x daily	50 mg 3x daily	CYP 2D6 substrate
	enalapril	5 mg daily	10-20 mg daily	40 mg daily	CYP 3A4 substrate
	ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	lisinopril	**5 mg daily**	**10-20 mg daily**	**40 mg daily**	**No**
	fosinopril	10 mg daily	20 mg daily	40 mg daily	Yes (CYP450 unknown)
	Rarely used: **perindopril**	**4 mg daily**	**none**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
Angiotensin II Receptor Blockers (ARBs)	losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 substrate
	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	telmisartan	**40 mg daily**	**none**	**80 mg daily**	**Yes, but not CYP450**
	valsartan	**80 mg daily**	**none**	**160 mg daily**	**Yes, but not CYP450**
α and β Blocker	labetalol	100 mg twice daily	200 mg twice daily	400 mg twice daily	CYP 2D6 substrate and inhibitor

4.1.2 Management of specific everolimus toxicities

Overall, safety data available from completed, controlled and uncontrolled studies indicate that everolimus is generally well tolerated at weekly or daily dose schedules. The safety profile is characterized by manageable adverse events (AEs). These AEs are generally reversible and non-cumulative.

Adverse events most frequently observed with everolimus are stomatitis, rash, diarrhea, fatigue, infections, asthenia, nausea, peripheral edema, decreased appetite, headache, dysgeusia, epistaxis, mucosal inflammation, pneumonitis, weight decreased, vomiting, pruritus, cough, dyspnea, dry skin, nail disorder, and pyrexia. . Overall, the most frequently observed laboratory abnormalities include decreased hematology parameters including hemoglobin, lymphocytes, platelets, and neutrophils (or collectively as pancytopenia).; increased clinical chemistry parameters including cholesterol, triglycerides, glucose, aspartate transaminases, creatinine, alanine transaminases, and bilirubin; and decreased clinical chemistry parameters including phosphate and potassium. The majority of these AEs have been of mild to moderate severity (NCI CTC grade 1-2).

4.1.2.1 Management of infections

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis and viral infections including reactivation of hepatitis B virus, have been described in patients taking everolimus Some of these infections have been severe (e.g. leading to sepsis, respiratory or hepatic failure) and occasionally have had a fatal outcome.

Physicians and patients should be aware of the increased risk of infection with everolimus Treat pre-existing infections prior to starting treatment with everolimus. While taking everolimus, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of everolimus.

If a diagnosis of invasive systemic fungal infection is made, discontinue everolimus and treat with appropriate antifungal therapy.

Cases of pneumocystis jirovecii pneumonia (PJP), some with a fatal outcome, have been reported in patients who received everolimus. PJP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

4.1.2.2 Management of skin toxicity

For patients with grade 1 toxicity, no specific supportive care is usually needed or indicated. Rash must be reported as an AE. Patients with grade 2 or higher toxicity may be treated with the following suggested supportive measures at the discretion of the investigator: oral minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisolone (short course), topical corticosteroids, or pimecrolimus.

4.1.2.3 Management of Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus.

4.1.2.4 Angioedema with concomitant use of angiotensin-converting enzyme (ACE) inhibitors

Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment).

4.1.2.5 Renal Failure Events

Cases of renal failure (including acute renal failure), some with fatal outcome, occurred in patients treated with everolimus. Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function.

Elevations of serum creatinine, usually mild, and proteinuria have been reported in patients taking everolimus. Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein, or serum creatinine, is recommended prior to the start of everolimus therapy and periodically thereafter.

4.1.2.6 Management of stomatitis / oral mucositis / mouth ulcers

Adverse Drug Reaction	Severity	Everolimus Dose Adjustment and Management Recommendations
Stomatitis	Grade 1 (Minimal symptoms, normal diet)	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day.
	Grade 2 (Symptomatic but can eat and swallow modified diet)	Temporary dose interruption until recovery to grade ≤1. Re-initiate everolimus at the same dose. If stomatitis recurs at grade 2, interrupt dose until recovery to grade ≤1. Re-initiate everolimus at one dose level lower. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste)*.
	Grade 3 (Symptomatic and unable to adequately eat or hydrate orally)	Temporary dose interruption until recovery to grade ≤1. Re-initiate everolimus at one dose level lower. Manage with topical analgesic mouth treatments (i.e. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste)*
	Grade 4 (Symptoms associated with life-threatening consequences)	Discontinue everolimus and treat with appropriate medical therapy.

* using agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

Patients with a clinical history of stomatitis/mucositis/mouth ulcers and those with gastrointestinal morbidity associated with mouth/dental infections, irritation of esophageal mucosa e.g. gastroesophageal reflux disease (GERD) and pre-existing stomatitis/mucositis must be monitored even more closely. Patients should be instructed to report the first onset of buccal mucosa irritation/reddening to their study physician immediately.

Stomatitis/oral mucositis/mouth ulcers due to everolimus should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with everolimus as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. The suggested paradigm for treatment of stomatitis/oral mucositis/mouth ulcers is as follows:

1. For mild toxicity (grade 1), no dose adjustment required. Manage with non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
2. For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral

alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).

3. Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. These agents should be avoided.
4. Antifungal agents should be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of everolimus metabolism, therefore leading to higher everolimus exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed.

4.1.2.7 Management of diarrhea

Appearance of grade 1-2 diarrhea attributed to study drug toxicity may be treated with supportive care such as loperamide, initiated at the earliest onset (for example 4 mg orally followed by 2 mg orally every 2 hours until resolution of diarrhea).

4.1.2.8 Management of hyperlipidemia and hyperglycemia

Adverse Drug Reaction	**Severity**	**Everolimus Dose Adjustment and Management Recommendations**
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
	Grade 3	Temporary dose interruption. Re-initiate everolimus at one dose level lower. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue everolimus and treat with appropriate medical therapy.

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits of the patient. Grade 2 or higher hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or grade 2 hypertriglyceridemia or higher (>2.5x upper normal limit) should be treated with a 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g. atorvastatin, pravastatin, fluvastatin) or appropriate triglyceride-lowering medication, in addition to diet.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine phosphokinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

Dyslipidemia (including hypercholesterolemia and hypertriglyceridemia) has been reported in patients taking everolimus. Monitoring of blood cholesterol and triglycerides prior to the start of everolimus therapy and periodically thereafter as well as management with appropriate medical therapy is recommended.

Hyperglycemia has been reported in patients taking everolimus. Monitoring of fasting serum glucose is recommended prior to the start of everolimus and periodically thereafter. More frequent monitoring is recommended when everolimus is co-administered with other drugs that may induce hyperglycemia. Optimal glycemic control should be achieved before starting a patient on everolimus.

4.1.2.9 Management of non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking everolimus. Some of these have been severe and on rare occasions, a fatal outcome was observed.

- A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Opportunistic infections such as PJP should be ruled out in the differential diagnosis of non-infectious pneumonitis. Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue everolimus therapy without dose alteration.

If symptoms are moderate (grade 2), consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Everolimus may be reintroduced at a daily dose approximately 50% lower than the dose previously administered.

For cases of grade 3 non-infectious pneumonitis, interrupt everolimus until resolution to less than or equal to grade 1. Everolimus may be re-initiated at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances. If toxicity recurs at grade 3, consider discontinuation of everolimus. For cases of grade 4 non-infectious pneumonitis, everolimus therapy should be discontinued. Corticosteroids may be indicated until clinical symptoms resolve.

For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for pneumocystis jirovecii pneumonia (PJP) may be considered. The two compounds studied most extensively for prophylaxis against PJP have been trimethoprim-sulfamethoxazole, given orally, and pentamidine, given as an aerosol.

If non-infectious pneumonitis develops, the guidelines should be followed. Consultation with a pulmonologist is recommended for any case of pneumonitis that develops during the study.

Management of non-infectious pneumonitis

Worst grade pneumonitis	Suggested investigations	Management of pneumonitis	Everolimus dose adjustment
Grade 1 (Asymptomatic, radiographic findings only)	CT scans with lung windows.	No specific therapy is required	No dose adjustment required. Initiate appropriate monitoring.
Grade 2 (Symptomatic, not interfering with Activities of Daily Living)	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Consider a bronchoscopy with biopsy and/or BAL. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence.	Symptomatic only. Consider corticosteroids and/or other supportive therapy if symptoms are troublesome.	Rule out infection and consider interruption of everolimus until symptoms improve to Grade ≤ 1. Re-initiate everolimus at one dose level lower. Discontinue everolimus if failure to recover within ≤ 28 days.
Grade 3 (Symptomatic, Interfering with Activities of Daily Living. O2 indicated	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and interrupt everolimus until symptoms improve to Grade ≤ 1. Consider re-initiating everolimus at one dose level lower. Discontinue everolimus if failure to recover within ≤ 28 days. If toxicity recurs at Grade 3, consider discontinuation
Grade 4 (Life-threatening, ventilatory support indicated)	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and discontinue everolimus.

4.1.2.10 Management of hepatitis reactivation / flare

Reactivation of Hepatitis B (HBV) has been observed in patients with cancer receiving chemotherapy[98]. Sporadic cases of Hepatitis B reactivation have also been seen in this setting with everolimus. Use of antivirals during anti-cancer therapy has been shown to reduce the risk of Hepatitis B virus reactivation and associated morbidity and mortality[99]. A detailed assessment of Hepatitis B/C medical history and risk factors must be done for all patients at baseline, with testing performed prior to the first dose of study drug.

Monitoring and prophylactic treatment for hepatitis B reactivation

Table 11 provides detail of monitoring and prophylactic therapy according to the baseline results of viral load and serologic markers testing.

Table 11 Action to be taken based on screening hepatitis B results

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBsAb	+ or -	+ or -	+ and no prior HBV vaccination	+ or -	- or + with prior HBV vaccination
HBcAb	+ or -	+ or -	+ or -	+	-
Recommendation	Prophylaxis treatment should be started 1-2 weeks prior to first dose of everolimus Monitor HBV-DNA approximately every 4-8 weeks		No prophylaxis Monitor HBV-DNA approximately every 3-4 weeks		No specific action

Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of everolimus. For HBV reactivation definition and management guidelines, see **Table 12**.

Table 12 Guidelines for the management of hepatitis B reactivation

HBV reactivation (with or without clinical signs and symptoms)*	
For patients with baseline results: Positive HBV-DNA **OR** positive HBsAg --- **reactivation is defined as:** [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA]	**Treat**: Start a second antiviral medication AND Interrupt everolimus administration until resolution: • ≤ baseline HBV-DNA levels **If resolution occurs within ≤ 28 days**, everolimus should be re-started at one dose lower, if available. (see **Table 7** for dose levels available) If the patient is already receiving the lowest dose of everolimus according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of everolimus. **If resolution occurs > 28 days** Patients should discontinue everolimus but continue both antiviral therapies at least 4 weeks after last dose of everolimus.
For patients with baseline results: Negative HBV-DNA **and** HBsAg **AND** **[**Positive HBsAb (with no prior history of vaccination against HBV), **OR** positive HBcAb**]** --- **Reactivation is defined as:** New appearance of measurable HBV-DNA	**Treat:** Start first antiviral medication AND **Interrupt** everolimus administration until resolution: • ≤ undetectable (negative) HBV-DNA levels **If resolution occurs within ≤ 28 days**, everolimus should be re-started at one dose lower, if available (see **Table 7** for dose levels available). If the patient is already receiving the lowest dose of everolimus according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of everolimus. **If resolution occurs > 28 days** Patients should discontinue everolimus but continue antiviral therapy at least 4 weeks after last dose of everolimus.

* All reactivations of HBV are to be recorded as grade 3 (e.g. CTCAE Version 4.0 - Investigations/Other: Viral Reactivation), unless considered life threatening by the investigator, in which case they should be recorded as grade 4. Date of viral reactivation is the date on which the rise or reappearance of HBV-DNA was recorded.

Monitoring for hepatitis C flare

The following two categories of patients should be monitored every 4–8 weeks for HCV flare:

- Patients with detectable HCV RNA-PCR test at screening.
- Patients known to have a history of HCV infection, despite a negative viral load test at screening (including those that were treated and are considered ‘cured’)

For definitions of HCV flare and actions to be taken in the event of a flare, please refer to **Table 13**.

Table 13 Guidelines for the management of hepatitis C flare

Baseline results	HCV flare definition*	HCV flare management
Detectable HCV-RNA	> 2 $\log_{10}$ IU/mL increase in HCV-RNA **AND** ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue everolimus
Knowledge of past hepatitis C infection with no detectable HCV-RNA	New appearance of detectable HCV-RNA **AND** ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue everolimus

* All flares of HCV are to be recorded as grade 3 (e.g. CTCAE Version 4.0 - Investigations - Other: Viral Flare), unless considered life threatening by the investigator; in which case, they should be recorded as grade 4. Date of viral flare is the date on which both the clinical criteria described above were met. (e.g., for a patient whose HCV-RNA increased by 2 logs on 01 JAN 2011 and whose ALT reached > 5 x ULN on 22 JAN 2011, the date of viral flare is 22 JAN 2011).

4.2 CONCURRENT MEDICATIONS

4.2.1 General guidelines

Patients must be instructed not to take any medications (over-the-counter or other products) during the protocol treatment period without prior consultation with the investigator. The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) taken within 28 days of starting study treatment through the 30-day safety follow up visit should be reported on the CRF.

4.2.2 Cytochrome P450 and P-glycoprotein inhibitors/inducers/substrates

Co-administration of everolimus or sunitinib with strong inhibitors of CYP3A4 or PgP should be avoided; and may cause increased drug concentrations. For a current table of Substrates, Inhibitors and Inducers please access the following website:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Everolimus is metabolized by CYP3A4 in the liver and to some extent in the intestinal wall.

Therefore, the following are recommended:

- Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) inhibitor should be avoided.
- Co-administration of either study drug with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be used with caution. If a patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of everolimus by approximately 50%. Additional dose reductions to every other day may be required to manage toxicities. If the inhibitor is discontinued, the everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor after a washout period of 2 to 3 days.

- Grapefruit, Seville oranges, and starfruit affect P450 and PgP activity. Concomitant use should be avoided.
- If patients require co-administration of a strong CYP3A4 inducer with everolimus, consider doubling the daily dose of everolimus (based on pharmacokinetic data), using increments of 5 mg or less. This dose of everolimus is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before the everolimus dose is returned to the dose used prior to initiation of the strong CYP3A4 inducer.
- This dose adjustment of everolimus is intended to achieve similar AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the everolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.

Please refer to **Table 14** listing relevant inducers and inhibitors of CYP3A and **Table 15** for a list of relevant substrates, inducers, and inhibitors of PgP.

4.2.2.1 Everolimus and drugs influencing CYP3A4 enzyme

Everolimus is a substrate of CYP3A4, and a substrate and moderate inhibitor of the multidrug efflux pump, PgP (PgP, MDR1, and ABCB1). Therefore, extent of absorption and subsequent elimination of systemically absorbed everolimus may be influenced by products that are substrates, inhibitors, or inducers of CYP3A4 and/or PgP. Concurrent treatment with strong CYP3A4-inhibitors should be avoided. Inhibitors of PgP may decrease the efflux of everolimus from brain or tumor and therefore increase everolimus concentrations in these tissues. In vitro studies showed that everolimus is a competitive inhibitor of CYP3A4 and of CYP2D6, potentially increasing the concentrations of products eliminated by these enzymes. Thus, caution should be exercised when co-administering everolimus with CYP3A4 and CYP2D6 substrates with a narrow therapeutic index. Clinical studies have been conducted in healthy subjects to assess pharmacokinetic drug interactions between everolimus and potential CYP3A modifiers (ketoconazole, verapamil, erythromycin, rifampin, midazolam, and HMGCoA reductase inhibitors (statins).

Table 14 Clinically relevant drug interactions: inducers, and inhibitors of isoenzyme CYP3A

Inducers
Strong inducers: avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum) **Moderate inducers:** bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, [talviraline], thioridazine, tipranavir **Weak inducers:** amprenavir, aprepitant, armodafinil (R-modafinil), bexarotene, clobazam, danshen, dexamethasone, Echinacea, garlic (allium sativum), gingko (ginkgo biloba), glycyrrhizin, methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, prednisone, [pleconaril], primidone, raltegravir, rufinamide, sorafenib, telaprevir, terbinafine, topiramate, [troglitazone] , vinblastine
Inhibitors
Strong inhibitors: boceprevir, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole[100], ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandamycin, voriconazole **Moderate inhibitors:** Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, grapefruit juice (citrus parasidi fruit juice), imatinib, schisandra sphenanthera, tofisopam, verapamil

Table 15 Clinically relevant drug interactions: substrates, inducers, inhibitors of PgP and PgP/CYP3A dual inhibitors

Substrates
colchicine, digoxin, fexofenadine, indinavir, paclitaxel, talinolol, topotecan, vincristine, everolimus
Inducers
rifampin, St John's wort
PgP Inhibitors and PgP/CYP3A Dual Inhibitors
amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fexofenadine, fluvoxamine, ginkgo (ginkgo biloba), indinavir, itraconazole, lopinavir, mibefradil, milk thistle (silybum marianum), nelfinavir, nifedipine, nitrendipine, paroxetine, quercetin, quinidine, ranolazine, rifampin, ritonavir, saquinavir, Schisandra chinensis, St John's wort (hypericum perforatum), talinolol, Telaprevir, telmisartan, ticagrelor, tipranavir, tolvaptan, valspodar, verapamil
Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Oct. 2, 2011,29-Oct-2012 which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies", the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table.

4.2.3 Vaccinations

Immunosuppressants may affect the response to vaccination and vaccination during treatment with everolimus may therefore be less effective. The use of live vaccines should be avoided during treatment with everolimus. For pediatric patients with SEGA that do not require immediate treatment, complete the recommended childhood series of live virus vaccinations prior to the start of therapy according to local treatment guidelines. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

5 BIOSPECIMEN COLLECTION

5.1 SAMPLE COLLECTION FOR GENOTYPING AND RESEARCH STUDIES

5.1.1 Tumor Sample

Within 4 weeks prior to initiation of treatment with the respective study agent (everolimus or sunitinib), patients who meet eligibility criteria, will undergo biopsy of the primary tumor or any metastatic site for molecular analyses. Patients will undergo a percutaneous core needle (16 or 18 gauge) biopsy of the tumor under local anesthesia if there are no paraffin blocks available of tumor sample previously removed or biopsied. These percutaneous biopsies will be performed by interventional radiology (CT scan or ultrasound guidance). If needed, patients will be offered conscious sedation for the biopsy procedure. Sample collection will be performed according to standard operating procedures. Four core needle biopsies will be obtained, three samples will be formalin fixed and sent to the Laboratory of Pathology in the NCI for histological study. The official pathology report and samples will then be taken to Dr. Paul Meltzer's laboratory:

Paul Meltzer, Email: paulmeltzer@mail.nih.gov

CANCER GENETICS BRANCH

Bldg. 37/Room 6183,

Bethesda, MD 20892,

Phone: 240-760-6136

The remaining sample will be immediately placed in cryovials, snap frozen on liquid nitrogen or dry ice and transported to Dr. Naris Nilubol's laboratory.

Fresh tissue samples should be collected into empty, unused cryovials (Nunc catalog #5001-0012, 5001-1020 or equivalent) on dry ice or liquid nitrogen. Samples may be obtained by FNA or core biopsy.

The interval between sample acquisition and freezing on dry ice must not exceed 30 minutes. Frozen, vialed samples should be transferred from dry ice to -80°C (minimum) or liquid nitrogen frozen storage within 2 hours.

Samples will be recorded in LabMatrix and reviewed by the Laboratory of Pathology to confirm the diagnosis. The remaining sample will be transported to Dr. Paul Meltzer's laboratory [Paul Meltzer, M.D., Bldg. 37/Room 6138, Bethesda, MD 20892, Phone: 240-760-6136, Email: pmeltzer@mail.nih.gov] for tumor genotyping along the saliva DNA.

5.1.2 Saliva Collection and Peripheral Blood

Saliva specimen (2-13 ml) will be obtained for targeted sequencing and comparison to tumor sequencing results and mutation calls before treatment. The saliva samples will be collected by a saliva collecting kit with complete and detailed instructions for collection available in the kit and on manufacturer's website at http://www.dnagenotek.com/ROW/products/OG500.html (an alternative saliva collecting kit can be used if needed). The saliva will be processed by and stored in the laboratory of Dr. Paul Meltzer and will be used as an autologous control for future genomic studies.

3 mL of saliva will be collected using the Oragene saliva collection kit (DNA Genotek). The sample may be collected at any time after informed consent has been obtained, but collection is preferred at baseline.

Ideally, the patient should be advised not to eat or drink anything 30 minutes prior to collection.

Once the sample is obtained, the top of the device is closed, releasing a preservative, the top is removed, and a cap is placed on the tube.

The date and exact time of the collection should be recorded on the sample.

Samples will be recorded in LabMatrix. DNA will be extracted from the saliva samples and the DNA sample (along with the coded, linked tumor sample) will be transported to Dr. Paul Meltzer's laboratory. Dr. Meltzer will not have access to the sample code key.

Peripheral blood (30 mL) may be obtained for targeted sequencing and comparison to tumor sequencing results and mutation calls after enrollment and before treatment. The blood will be processed by and stored in the laboratory of Dr. Paul Meltzer and will be used as an autologous control for future genomic studies.

Test/assay	**Volume (approx.)**	**Type of tube**	**Collection point**	**Location of specimen analysis**
Molecular Analysis	4 Core Tumor Biopsies		Screening	Dr. Paul Meltzer's lab
Targeted Sequencing & Autologous Control	2-13 ml Saliva	Saliva Collecting Kit	Baseline	Dr. Paul Meltzer's lab
Targeted Sequencing	30 ml Serum		Baseline	Dr. Paul Meltzer's lab

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

5.2.1 Procedures for Storage of Specimens in the Laboratory of Dr. Naris Nilubol

- In patients who undergo biopsy, the samples will be immediately snap frozen in liquid nitrogen and transported to the Dr. Naris Nilubol Lab by calling 240-760-6155. Samples will be labeled with the date and time of acquisition, the type of tissue and patient study ID. Upon receipt in the lab, samples will be bar coded and logged in to the tissue

database, LabMatrix. Samples will be stored in -20°C or -80°C freezers until molecular analysis. All freezers are monitored and are on separate emergency generator lines.

- Saliva and serum samples for correlative studies may also be obtained and will be stored and tracked in the same manner as tissue samples.
- At the completion of the protocol, the investigator will dispose of all specimens in accordance with the environmental protection laws, regulations and guidelines of the Federal Government and the State of Maryland.
- Samples at NIH will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without IRB notification and an executed MTA.
- All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. The PI will report any loss or destruction of samples to the NIH IRB as soon as he is made aware of such loss
- If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.
- The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

5.2.2 Procedures for Storage of Tissue Specimens in the Laboratory of Pathology

Tissues designated for clinical diagnostics are transported to the Laboratory of Pathology (LP) where they are examined grossly, and relevant portions are fixed, embedded in paraffin and sectioned and stained for diagnostic interpretation. Unutilized excess tissues are stored for up to three months, in accordance with College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations (CAP/JCAHO) guidelines, and then discarded. Following completion of the diagnostic workup, the slides and tissue blocks are stored indefinitely in the LP's clinical archives. All specimens are catalogued and retrieved utilizing the clinical laboratory information systems, in accordance with CAP/JCAHO regulations. The use of any stored specimens for research purposes is only allowed when the appropriate IRB approval has been obtained. In some cases, this approval has been obtained via the original protocol on which the patient was enrolled

5.3 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.3.1 Description of the scope of genetic/genomic analysis

- Tumor genotyping: Somatic mutation analysis of tumor biopsy specimens will be performed by sequencing 197 driver genes (**Appendix C**) in a CLIA certified genetic laboratory.
- Germline sequencing for 197 driver genes (**Appendix C**) will be performed on saliva samples or peripheral blood samples in a CLIA certified genetic laboratory
- Histology: Tissues may be examined by standard histology, immunohistochemistry and or in situ hybridization in the Laboratory of Pathology, NCI.

5.3.2 Privacy and Confidentiality of medical information/biological specimens

Fresh tumor and blood samples will be stored in a minus 80-degree freezer. The samples of each patient will be assigned a study ID number, and that number will be used in all laboratory studies. At no time will patient's names be used on the blood and tissue samples. The molecular studies will be done in the CLIA certified genetic laboratory of Paul Meltzer, MD. Sometimes, because a group collaboration or journal policy requires it, a subject's genetic data may be deposited in a database such as dbGaP. Although there is controlled access to such a database, such a submission carries theoretical risks of revealing the identity of the subject. This is discussed in the consent.

5.3.3 A Certificate of Confidentiality will be obtained for the study as described in Section **10.3.1.5.**

5.3.4 Management of Results

The results of molecular studies will be communicated to the patient. Other than initial determination of the presence of particular genetic alteration(s) outlined in **Appendix C** and **Appendix D**, the results of subsequent molecular studies are for research purposes only and will not be communicated to the patient. The exceptions to this are potential incidental findings that are deemed medically significant and actionable.

Subjects, treated in NCI will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists). Subjects who still remain on the study will be contacted at this time with a request to provide a blood sample to be sent to a CLIA certified laboratory.

5.3.4.1 Genetic counseling in NCI

If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH (at our expense) to have genetic education and counseling with the NCI Genetics Branch to explain this result. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense). This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into a password protected electronic system (NCI C3D) and ensuring data accuracy, consistency and timeliness. Clinical data will be entered into the NCI C3D electronic database at least once every two weeks when patients are enrolled on the trial. Protocol-specific eCRFs will be developed for this trial in C3D. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts.

All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

The NCI investigators will be responsible for the collection, maintenance, and quality control of the study data.

Labmatrix will be used for sample data collection. Data in this system will be entered by the NCI staff.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be followed for adverse events for at least 30 days after removal from study treatment or until off-study, whichever comes first.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

6.1.1 Source Documents

The PI will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s), providing direct access to source documents.

6.1.2 Case Report Forms

Data may be entered from the source documents directly into eCRFs in C3D for each patient enrolled in this study. The principal investigator or research nurse will review the eCRFs for completeness and accuracy. Site personnel may also conduct independent audits to ensure completeness and accuracy of data in C3D.

Only the following adverse events will be recorded on the Case Report Form:

- Grade 2 unexpected events that are possibly, probably or definitely related to the study drugs;
- Grade 3 and 4 events that are possibly, probably or definitely related to the study drugs;
- Grade 5 events regardless of attribution;
- Serious Events regardless of attribution.

Patients who meet the standard of care criteria for resection of their disease will undergo a major operative procedure and may receive extensive care in the ICU. The principal investigator or designee will closely monitor and document the clinical care and treatment of each patient as per standard of care at the NIH Clinical Center. As per NIH Clinical Center standards of practice, the Occurrence Reporting System will be used to report any clinical events meeting these reporting criteria.

6.1.3 Data Quality Assurance

The research team will monitor each patient's dataset throughout the study. Source document review will be made against entries on the eCRF and a quality assurance check will be performed to ensure that the investigator is complying with the protocol and regulations. In addition, after the research team (data managers) completes the CRFs a research nurse or physician at the NCI will review and verify the data.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

- Coded, linked data in an NIH-funded or approved public repository.
- Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

How and where will the data be shared?

Data will be shared through:

- An NIH-funded or approved public repository. Clinicaltrials.gov.
- BTRIS
- Publication and/or public presentations.

When will the data be shared?

- Before publication.
- At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response every 12 weeks.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.3.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with sunitinib or everolimus.

Evaluable for objective response: Only those patients who according to RECIST guideline (version 1.1) have measurable disease present at baseline, have been started on therapy with everolimus or sunitinib, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have been started on therapy with everolimus or sunitinib, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.3.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as:

- By chest x-ray: ≥20 mm;
- By CT scan:
    - Scan slice thickness 5 mm or under as ≥10 mm with CT scan
    - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam: ≥10 mm.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Metastatic lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered

non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. 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 only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.3.3 Methods for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique will be used to characterize each identified and reported lesion at baseline and during follow-up.

Conventional CT: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Tumor markers: Chromogranin A levels, which represents a constitutive neuroendocrine secretory protein, is the most widely accepted biomarker. Chromogranin A was compared to a panel of biomarkers and proved to be the most accurate, with a specificity of 85.7% and sensitivity of 67.9%[101]. Chromogranin A is elevated in 60- 80% of patients with neuroendocrine tumors. The National Cancer Institute (NCI) recommends that serial

measurements of CgA be incorporated into prospective clinical trials[49]. Chromogranin A level will be checked within 2 weeks prior to treatment, and every 3 months after treatment initiation.

68-Gallium DOTATATE: We and others have demonstrated that 68-Gallium DOTATATE is more sensitive for detecting sites of metastatic disease than anatomic imaging studies [102]. Therefore, we will also use 68-Gallium DOTATATE imaging results that show new lesions within 18 months follow up time to define progression of disease. All patients must have a target lesion as identified by conventional CT or MRI, however, to be eligible for enrollment in the study to evaluate response by RECIST criteria.

6.3.4 Response Criteria

6.3.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

6.3.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance 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. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.3.4.3 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 progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

6.3.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

6.3.6 Progression-Free Survival

PFS is defined as the duration of time from start of each treatment to time of progression or death, whichever occurs first.

6.3.7 Response Review

Simultaneous review of the patients' files and radiological images for all responses will be reviewed by an expert(s) independent of the study at the study's completion.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- 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 a serious adverse drug experience 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.

7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; AND
- Is related or possibly related to participation in the research; AND
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NIH INTRAMURAL IRB AND CLINICAL DIRECTOR REPORTING

7.2.1 NIH Intramural IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NIH Intramural IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.2.2 NIH Intramural IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NIH Intramural IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

   NOTE: Grade 1 events are not required to be reported.

7.2.3 NIH Intramural IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NIH Intramural IRB.

7.3 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

7.3.1 Novartis

The Principal Investigator will notify Novartis of each Serious Adverse Event (SAE) as defined under 21 CFR 310.305 encountered in the Clinical Trial within 24 hours of becoming aware of it. This applies to SAEs which occur after the patient takes the first dose of study drug and continues until at least 30 days after the patient has stopped study treatment or until the patient is taken off-study, whichever comes first. Information about all SAEs is collected and recorded on the Novartis Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The PI must assess and record the relationship of each SAE to each specific study treatment, complete the SAE Report Form and send the completed, signed form along with the Novartis provided fax cover sheet to the Novartis Oncology Drug Safety and Epidemiology (DS&E) department by fax (877-778-9739) or email (clinicalsafetyop.phuseh@novartis.com) within 24 hours of PI's awareness.To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up 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 newborn complications.

Pregnancy should be reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E) by fax (877-778-9739) or email (clinicalsafetyop.phuseh@novartis.com). Pregnancy follow-up should include an assessment of the possible relationship to the investigational/study treatment and 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.

7.3.2 Pfizer

The Principal Investigator will notify Pfizer of each Serious Adverse Event (SAE) encountered in the Clinical Trial within 24 hours of becoming aware of it, even if complete information is not yet available. This applies to SAEs which occur after the patient takes the first dose of study drug and continues until at least 30 days after the patient has stopped study treatment or is taken off-study, whichever comes first. Additionally, the Principal Investigator will notify Pfizer of any SAE the PI suspects has a causal relationship between the Pfizer Product and the SAE at any time after the patient's last study treatment. Information about all SAEs is collected and recorded on the Pfizer-provided Investigator-Initiated Research Serious Adverse Event Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The PI must assess and record the relationship of each SAE to each specific study treatment, complete the SAE Report Form and send the completed, signed form along with the Pfizer Reportable Event Fax Cover Sheet to the Pfizer US Drug Safety Unit fax number 866-997-8322 within 24 hours of PI's awareness. To ensure patient safety, the Principal Investigator will also report each pregnancy, drug exposure during lactation, occupational exposure, and reportable instances of lack of effect as SAEs to Pfizer.

7.4 DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 STATISTICAL CONSIDERATIONS

The primary objective of this trial is to determine PFS of patients with low- or intermediate grade NET who receive first-line targeted therapy. This will provide preliminary data to explore whether the PFS on first-line therapy in patients treated with sunitinib or everolimus based on tumor genotyping may represent a potential improvement over published results with regular treatment with everolimus/sunitinib. Secondary objectives include evaluation of response and OS as well as safety and exploring the association between tumor genotype and PFS, and response to treatment.

If the findings suggest improved PFS from targeted treatment, a larger randomized trial to confirm the findings will be developed.

Following tumor genotyping, eligible patients will be treated with everolimus (Arm 2) or sunitinib (Arm 1). Based on results of the genotyping, enrolled patients will then receive targeted treatment with sunitinib (for mutations in *MEN1/PDGFR/KIT/FTL3* or everolimus (for mutations in *NF1/PTEN/ PI3K/AKT/mTOR/VHL*). Patients with other different mutations or multiple types of mutations will be assigned to receive sunitinib since almost all of these tumors have elevated levels of VEGF/VEGFR expression.

Results from previously published trials[53, 55] both demonstrated approximately 11 months PFS in patients similar to the ones to be treated on this protocol. Those patients had not received cytoreductive surgery, and also were not assigned to receive treatment on the basis of any tumor genotype information. In the context of this trial, the study will be designed to determine if meaningful improvement in PFS may be obtained using this focused strategy. For purposes of sample size determination, patients will be primarily evaluated based on the treatment received. Thus, within each treatment arm, using the method of Brookmeyer and Crowley, with 44 patients accrued during a 48-month period (88 total patients for the two arms), and followed for up to an additional 12 months (60 months total from entry of the first patient), there would be 80% power to test whether the median PFS is consistent with 18 months, and greater than 11 months, with a 0.10 alpha level one-sided significance test.

In practice, a Kaplan-Meier curve of PFS will be constructed for each arm and will have the median as well as key time points such as 12 and 18 months estimated, along with appropriate

80% and 95% confidence intervals to explore whether the present results exceed those from prior studies. In addition, the Kaplan-Meier curves for all patients who received either sunitinib and everolimus as their treatments may be combined into one pooled Kaplan-Meier curve if the two curves for these treatments are sufficiently similar to one another ($p>0.30$ by a two-tailed log-rank test). This combined curve will then be evaluated relative to the published median of 11 months PFS for each arm to provide a more powerful comparison relative to the historically expected results. In addition, Kaplan-Meier curves limited to the patients who received targeted therapy based solely on mutation status may be constructed for exploratory and descriptive purposes.

Response and overall survival will also be evaluated as secondary endpoints, based on the patients treated with sunitinib or everolimus, using all patients receiving treatment. These results will be descriptive and may consist of fractions of responses as well as Kaplan-Meier curves for survival. The association between genotype and PFS will be explored by evaluating the results within a treatment based on the major genotype categories identified. Safety will be evaluated by tabulating and reporting the distribution of the worst grade of each type of toxicity found, per patient, separately by arm. Should any particular type of toxicity result in 5 or more patients with grade 3-4 toxicity, a comparison of the distributions of toxicity between the two arms may be performed using a Cochran-Armitage test for trend.

Because the patients may not end up being assigned in equal proportions to the two arms, and because the goal is to have 44 evaluable patients who have received each treatment, additional patients beyond the 44 described above may be enrolled on the arm with faster accrual. As such, the study will have an accrual ceiling of 120 patients, with accrual ending when there are 44 evaluable patients on the arm with fewer patients. An amendment may also be needed if a lower proportion of patients than expected receive study drug therapy or if a high portion of treated patients are not evaluable for response. It is anticipated that 20-30 patients per year may enroll onto this trial; thus, accrual may be completed in 4-5 years.

9 COLLABORATIVE AGREEMENTS

9.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

The everolimus used in this trial in NCI will be obtained under a CRADA (02975) with Novartis, the manufacturer of the agent.

9.2 CLINICAL TRIALS AGREEMENT (CTA)

The sunitinib used in this trial in NCI will be obtained under CTA with Pfizer (00963-14), the manufacturer of the agent.

10 HUMAN SUBJECTS PROTECTIONS

10.1 RATIONALE FOR SUBJECT SELECTION

Subjects from both gender groups and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. Efforts will be made to extend accrual to a representative population.

10.2 PARTICIPATION OF CHILDREN

Patients age 18 and older will be eligible for this study. The incidence and prevalence of metastatic pancreatic and gastrointestinal neuroendocrine tumors in the pediatric patient population is exceedingly rare and this is the rationale for not including this patient population.

10.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (Section **10.5**), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIHMEC Policy 87-4 and NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

10.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

10.4.1 Risks/Benefits Analysis

The risks and benefits of participation for adults who become unable to consent, are no different than those described for patients who are less vulnerable.

10.4.1.1 Risks

10.4.1.1.1 Study Drug Risks

The risks of participation in this study are primarily associated with the toxicities of the study agents as discussed in Section **11**. Both study agents have been approved by the FDA for the treatment of progressive, locally advanced or metastatic pancreatic NETs and have been available for clinical use since 2011. Patients will be monitored routinely in order to minimize the risk of complications.

10.4.1.1.2 Specimen Collection Risks

Risks also include those associated with specimen collection include pain, bleeding and the possibility of infection at the sampling site. Risk of baseline biopsy: All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent. If patients suffer any physical injury as a result of the biopsy, immediate medical treatment is available at the enrolling center. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

10.4.1.1.3 Risk of Radiation

This research study involves exposure to radiation from one CT guided biopsy**.** This radiation exposure is not required for medical care and is for research purposes only. The amount of radiation received in this study is 0.80 rem which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the

United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. More information about radiation is available in the pamphlet, An Introduction to Radiation for NIH Research Subjects.

10.4.1.1.4 Non-Physical Risks of Genetic Research

- Risk of receiving unwanted information

Anxiety and stress may arise as a result of the anticipation that unwanted information regarding disease related DNA sequencing or disease tendencies, or misattributed paternity. Patients will be clearly informed that the data related to DNA sequencing and genetic analysis is coded, investigational and will not be shared with patients, family members or health care providers.

- Risk related to possibility that information may be released

This includes the risk that data related to genotype, DNA sequencing or risk for disease tendency or trait can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the patients, family members or health care providers, this risk will be included in the informed consent document.

- Risk to family or relatives

Family members or relatives may or may not want to be aware of familial tendencies or genetic risks of disease which may cause anxiety about possible future health problems. As previously noted, patients will be given the option in the consent document to be notified of any medically significant and actionable incidental findings.

10.4.1.1.5 Certificate of Confidentiality

As part of study efforts to provide confidentiality of subject information, this study will obtain a Certificate of Confidentiality which helps to prevent forced disclosure of personally identifiable research information. The Certificate of Confidentiality allows investigators on this trial to refuse to disclose identifying information related to the research participants, should such disclosure have adverse consequences for subjects or damage their financial standing, employability, insurability or reputation. The informed consent includes the appropriate coverage and restrictions of the Certificate of Confidentiality.

10.4.1.2 Benefits

Subjects participating in the study may benefit from the study drugs, both of which are indicated in the use of the diseases. Additional possible benefits are tumor shrinkage and reduced morbidity.

10.5 CONSENT PROCESS AND DOCUMENTATION

All patients who are being considered for this trial will undergo informed consent prior to being enrolled on the trial. The PI or associate investigator will perform the consenting process. Patients and family members when applicable will be asked to read the consent and will be encouraged to ask questions. It will be stated clearly that participation in the research study is voluntary and that participants can withdraw from the study without losing benefits they would otherwise be entitled to. Patients will be enrolled after the consent document has been signed. The informed consent process will be documented in the patient’s medical record and on the

informed consent document. This process will be performed by the local Principal Investigator or designee.

10.5.1 Procedure for Consent via Telephone

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator.

11 PHARMACEUTICAL INFORMATION

11.1 SUNITINIB

11.1.1 Source

Sunitinib is manufactured by Pfizer and will be provided to the NIH CC Pharmacy under a CRADA.

11.1.2 Toxicity

(Please see package insert for a complete list of toxicities)

In over 10,000 subjects with solid malignant tumors diarrhea (52.4%), fatigue (49.0%), nausea (42.7%), decreased appetite (38.5%), vomiting (33.9%), palmar-plantar erythrodysaesthesia syndrome (28.7%), hypertension (27.6%), stomatitis (26.0%), dysgeusia (25.9%), and mucosal inflammation (25.7%) were the most commonly reported treatment emergent adverse events.

Overall, 60.3% experienced treatment-related AEs of Grade 3, 4, or 5 severity; Grade 3 in 46.9% of subjects, Grade 4 and grade 5 in 11.9% and1.6% of subjects respectively. The most commonly reported were neutropenia (13.5%), fatigue (9.2%), thrombocytopenia (8.6%), palmar-plantar erythrodysaesthesia syndrome (7.4%), diarrhea (6.3%), hypertension (5.5%), and asthenia (5.0%).

Neutropenia (0.3%), fatigue (8.8%), palmar-plantar erythrodysaesthesia syndrome (7.4%), thrombocytopenia (6.8%), diarrhea (6.1%); and hypertension (5.4%) were the most commonly reported treatment-related AEs of Grade 3 severity. Neutropenia (3.2%), thrombocytopenia (1.8%), and anemia (0.9%) were the most commonly reported treatment-related AEs of Grade 4 severity. Pulmonary embolism, cardiac failure, death, cerebral hemorrhage, renal failure, myocardial infarction, hepatic failure, gastrointestinal hemorrhage, multi-organ failure, respiratory failure, pneumonia, septic shock, cardiac arrest, sepsis, sudden death, tumor hemorrhage, and hemorrhage, were among the Grade 5 treatment-related AEs reported in at least 3 subjects.

Boxed Warning:

SUTENT has been associated with hepatotoxicity, which may result in liver failure or death. Liver failure has been observed in clinical trials (7/2281 [0.3%]) and post-marketing experience.

Liver failure signs include jaundice, elevated transaminases and/or hyperbilirubinemia in conjunction with encephalopathy, coagulopathy, and/or renal failure. Monitor liver function tests (ALT, AST, bilirubin) before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

Safety in patients with ALT or AST >2.5 × ULN or, if due to liver metastases, >5.0 × ULN has not been established.

11.1.3 Formulation and preparation

Sunitinib malate capsules consist of hard gelatin capsules containing sunitinib malate equivalent to 12.5, 25 and 50 mg sunitinib together with mannitol, croscarmellose sodium, povidone, and magnesium stearate.

11.1.4 Stability and Storage

Sunitinib – will be stored in a closed container at room temperature (15 to 30°C), away from heat, moisture, and direct light.

11.1.5 Administration procedures

Please see Section **3.2.1**

11.1.6 Incompatibilities

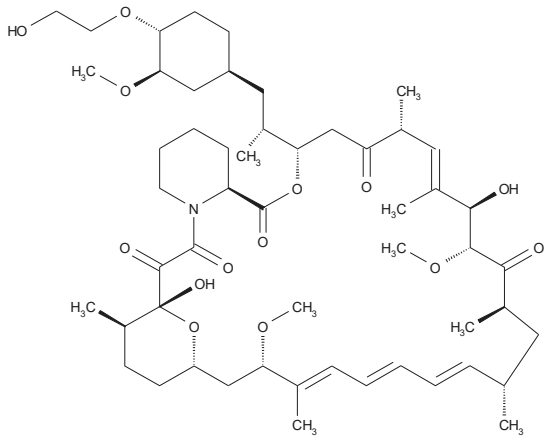
Co-administration of sunitinib with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib concentrations. Grapefruit may also increase plasma concentrations of sunitinib. A dose reduction for sunitinib should be considered when it must be co-administered with strong CYP3A4 inhibitors.

11.2 EVEROLIMUS

11.2.1 Drug substance

Chemical name	(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone
International non-proprietary name	Everolimus

11.2.2 Chemical structure



11.2.3 Source

Everolimus will be manufactured and provided to the NIH CC Pharmacy by Novartis under a Clinical Trials Agreement.

11.2.4 Toxicity

(Please see package insert for a complete list of toxicities)

Toxicity information is based on pooled safety data in cancer patients receiving everolimus (N=2470) in clinical studies including randomized, double-blind, placebo- or active comparator-controlled phase-III trials and phase-II studies related to the approved indications in oncology.

The most common ADRs (incidence ≥1/10 and suspected to be related to treatment by the investigator) from the pooled safety data were (in decreasing order): stomatitis, rash, fatigue, diarrhea, infections, nausea, decreased appetite, anemia, dysgeusia, pneumonitis, hyperglycemia, weight decreased, pruritus, asthenia, peripheral edema, hypercholesterolemia, epistaxis, and headache.

The most common grade 3/4 adverse drug reactions (incidence ≥1/100 to <1/10 and suspected to be related to treatment by the investigator) were stomatitis, anemia, hyperglycemia, fatigue, infections, pneumonitis, diarrhea, asthenia, thrombocytopenia, neutropenia, dyspnea, lymphopenia, proteinuria, hemorrhage, hypophosphatemia, rash, hypertension, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased and pneumonia.

The most common adverse events were stomatitis (in 64% of the patients in the everolimus group vs. 17% in the placebo group), rash (49% vs.10%), diarrhea (34% vs. 10%), fatigue (31% vs. 14%), and infections (23% vs. 6%). The most common grade 3 or 4 drug-related adverse events were anemia, hyperglycemia, stomatitis, thrombocytopenia, diarrhea, hypophosphatemia, and neutropenia[55].

11.2.5 Formulation and preparation

Dosage forms:	• **Tablets will be supplied in** 2.5 mg, 5

	mg, and 10 mg formulations • **Dispersible tablets (also referred to as 'tablets for oral suspension')**: 2 mg, 3 mg and 5 mg. The dispersible tablet is prepared as a suspension of undissolved medicine that is mixed with water, and then taken by mouth. The suspension can be prepared in an oral syringe or small drinking glass.
Composition/excipients:	• **Tablets:** Everolimus drug substance, butylhydroxytoluene/butylated hydroxytoluene (BHT), magnesium stearate, lactose anhydrous/Anhydrous lactose, lactose monohydrate, hypromellose/hydroxypropyl methylcellulose, crospovidone • **Dispersible tablets:** Everolimus drug substance, butylhydroxytoluene/butylated hydroxytoluene (BHT), magnesium stearate, lactose monohydrate, hypromellose/hydroxypropyl methylcellulose, crospovidone, silica colloidal anhydrous /colloidal silicon dioxide, mannitol/D-mannitol, cellulose microcrystalline/microcrystalline cellulose The excipients comply with the requirements of the applicable compendial monographs European Pharmacopeia (Ph. Eur.), Unites States Pharmacopeia / National Formulary (USP/NF).

11.2.6 Stability and Storage

Everolimus tablets and everolimus tablets for oral suspension are stored at 25°C (77°F); with excursions permitted between 15°–30°C (59°–86°F). Store everolimus in the original container, and protect from light and moisture.

11.2.7 Administration procedures

See Section **3.2.2**

11.2.8 Hazards and precautions

The extent of absorption of everolimus through topical exposure is not known. Therefore, caregivers are advised to avoid contact with suspensions of everolimus tablets or dispersible tablets. Wash hands thoroughly before and after preparation of either suspension.

11.2.9 Incompatibilities

Co-administration of everolimus with strong CYP3A4-inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir, boceprevir, telaprevir) and strong CYP3A4 inducers (e.g., rifampin, rifabutin) is not recommended without close monitoring of everolimus whole blood trough concentrations. Grapefruit and grapefruit juice inhibit cytochrome P450 3A4 and P-gp activity and should therefore be avoided with concomitant use of everolimus. Please refer to Section **4.2.2**

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13 Appendices

13.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

13.2 APPENDIX B: PREGNANCY AND ASSESSMENTS OF FERTILITY

There are no adequate data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects including embryo-toxicity and feto-toxicity. The potential risk for humans is unknown. Everolimus should not be given to pregnant women unless the potential benefit outweighs the potential risk to the fetus. If a pregnancy occurs while on study treatment, the newborn will be followed for at least 12 months.

It is not known whether everolimus is excreted in breast milk. However, in animal studies everolimus and/or its metabolites readily passed into the milk of lactating rats. Women taking everolimus should therefore not breast-feed.

Women of childbearing potential

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 8 weeks after stopping treatment. Highly effective contraception is defined as either:

- Total 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: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. 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 (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female subjects on the study, the vasectomised male partner should be the sole partner for that subject].
- Use of a combination of any two of the following (a+b or a+c or b+c):
  a. Use of oral, injected, implanted or other hormonal methods of contraception
  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
- In case of use of oral contraception, women should have been stable on the oral agent before taking study treatment.

Male Contraception

Sexually active males must use a condom during intercourse while taking the drug and for 8 weeks after stopping treatment and should not father a child in this period.

A condom is required to be used also by vasectomised men in order to prevent delivery of the drug via seminal fluid.

Female partners of male patients must also be advised to use one of the following contraception methods: Use of (1) oral, injected, implanted or other hormonal methods of contraception, or (2) intrauterine device (IUD) or intrauterine system (IUS), or (3) prior male/female sterilization.

Fertility

The potential for everolimus to cause infertility in male and female patients is unknown. However, menstrual irregularities, secondary amenorrhea and associated luteinizing hormone (LH)/follicle stimulating hormone (FSH) imbalance has been observed.
Based on non-clinical findings, male and female fertility may be compromised by treatment with everolimus.

13.3 Appendix C: Panel of 197 genes tested for in Clinical Molecular Profiling Core (CLIA-compliant). Genes implicated in NETs are in bold.

Genes

ABL1	*DMBT1*	*KRAS*	*RNF2*
ACN9	*DNMT3A*	*KRT20*	*RPS15*
ACVR1B	*DPYD*	*MAGI1*	*RUNX1*
AKT1	*EGF*	*MAP2K4*	*SCLC1*
ALK	*EGFR*	***MEN1***	*SDHA*
APC	*EGR3*	*MET*	*SDHAF1*
ARHGEF2	*EIF4G2*	*MGMT*	*SDHAF2*
ARID1A	*EML4*	*MIB1*	*SDHB*
ASXL1	*ENO1*	*MKI67*	*SDHC*
ATM	*ENO2*	*MLH1*	*SDHD*
ATRX	*ERBB2*	*MPL*	*SELT*
BAG3	*ERBB3*	*MSH2*	*SETD2*
BAI3	*ERBB4*	*MSH6*	*SLC38A1*
BAP1	*ERG*	*MUC1*	*SLC6A2*
BCAN	*EZH2*	*MUC17*	*SLTM*
BCL2	*F10*	*MUC2*	*SMAD4*
BRAF	*FAM123B*	*MUC3A*	*SMARCA4*
BRCA1	*FBXW7*	*MUTYH*	*SMARCB1*
BRCA2	*FGFR1*	*MVP*	*SMO*
CA12	*FGFR2*	*MYC*	*SMOX*
CA9	*FGFR3*	*MYD88*	*SMUG1*
CALU	*FH*	*NAT1*	*SOCS1*
CARD11	*FHIT*	*NAT2*	*SRC*
CBL	*FLCN*	*NES*	*SST*
CCND1	***FLT3***	***NF1***	*STC1*
CD34	*FOXL2*	*NF2*	*STK11*
CDC73	*FZR1*	*NOTCH1*	*SUFU*
CDH1	*GATA1*	*NOTCH2*	*SYP*
CDK4	*GATA2*	*NPM1*	*TCF7L2*
CDKN2A	*GATA3*	*NRAS*	*TET2*
CDX2	*GFAP*	*PBRM1*	*TFE3*
CEACAM7	*GNA11*	*PCNA*	*TFEB*
CEBPA	*GNAQ*	*PDGFRA*	*TMEM97*
CES3	*GNAS*	*PDZD4*	*TNFAIP3*
CHDM	*GRP*	*PGR*	*TNFSF13*
CRLF2	*GSTM1*	*PHOX2B*	***TP53***

CSF1R	*HIVEP3*	***PIK3CA***	*TPD52L2*
CSF3	*HNF1A*	*PMS2*	*TPM4*
CTNNA1	*HRAS*	*PPP2R1A*	***TSC1***
CTNNB1	*IDH1*	*PRCC*	***TSC2***
CUL2	*IDH2*	*PRKAR1A*	*TSHR*
CYLD	*IFNA1*	*PTCH1*	*TYK2*
CYP1A1	*IGKV1D-43*	***PTEN***	***VHL***
DAXX	*IL2*	*PTGS2*	*VIM*
DCC	*ITGB5*	*PTPN11*	*WT1*
DES	*JAK1*	*RB1*	*WTS*
DIRAS1	*JAK2*	*REEP5*	*XRCC1*
DIRC2	*JAK3*	*RET*	*ZNF135*
DKK3	*KDR*	*RNF139*	
DLD	*KIT*		

13.4 APPENDIX D: PATHWAY ANALYSIS OF 193 MAPPED GENES USING INGENUITY PATHWAY ANALYSIS*

Ingenuity Canonical Pathways	Molecules
AMPK Signaling	SRC,TSC1,PIK3CA,PPP2R1A,GNAS,AKT1,STK11,TSC2,SMARCA4,ATM,PRKAR1A
Angiopoietin Signaling	PIK3CA,AKT1,NRAS,PTPN11,HRAS,KRAS,ATM
EGF Signaling	MAP2K4,SRC,PIK3CA,JAK1,AKT1,EGF,HRAS,ATM,EGFR
Endothelin-1 Signaling	BRAF,MYC,SRC,PIK3CA,GNAS,NRAS,GNA11,GNAQ,HRAS,KRAS,PTGS2,ATM
Ephrin A Signaling	PIK3CA,PTPN11,ATM
Ephrin B Signaling	GNAS,CBL,GNA11,GNAQ,HRAS,CTNNB1
Ephrin Receptor Signaling	SRC,GNAS,AKT1,NRAS,PTPN11,GNA11,ABL1,GNAQ,EGF,HRAS,KRAS,JAK2
ErbB Signaling	MAP2K4,PIK3CA,AKT1,NRAS,ERBB4,EGF,HRAS,KRAS,ERBB3,ERBB2,ATM,EGFR
ErbB2-ErbB3 Signaling	PIK3CA,NRAS,TYK2,HRAS,KRAS,ERBB3,CCND1,PTEN,MYC,AKT1,ERBB2,JAK3,ATM
ErbB4 Signaling	PIK3CA,AKT1,NRAS,ERBB4,HRAS,KRAS,ATM
ERK/MAPK Signaling	BRAF,MYC,SRC,PIK3CA,PPP2R1A,NRAS,HRAS,KRAS,ATM,PRKAR1A
ERK5 Signaling	MYC,SRC,AKT1,NRAS,PTPN11,GNAQ,EGF,HRAS,KRAS,EGFR
Erythropoietin Signaling	SOCS1,SRC,PIK3CA,AKT1,NRAS,CBL,HRAS,KRAS,JAK2,ATM
Inhibition of Angiogenesis by TSP1	MAP2K4,TP53,AKT1,KDR
Insulin Receptor Signaling	TSC1,PIK3CA,JAK1,NRAS,HRAS,KRAS,JAK2,PTEN,AKT1,CBL,PTPN11,TSC2,PRKAR1A,ATM
mTOR Signaling	TSC1,PIK3CA,PPP2R1A,AKT1,NRAS,EIF4G2,STK11,TSC2,RPS15,HRAS,KRAS,ATM
p38 MAPK Signaling	MAP2K4,TP53,MYC,DAXX
PDGF Signaling	MYC,MAP2K4,SRC,PIK3CA,NRAS,JAK1,TYK2,PDGFRA,ABL1,HRAS,KRAS,JAK2,JAK3,ATM
PI3K/AKT Signaling	TP53,TSC1,PIK3CA,JAK1,NRAS,TYK2,HRAS,KRAS,JAK2,CCND1,PTEN,BCL2,PPP2R1A,AKT1,TSC2,PTGS2,JAK3,CTNNB1
Protein Kinase A Signaling	GNAS,PTCH1,GNAQ,HNF1A,PTEN,BRAF,PTPN11,DCC,SMO,SMAD4,PTGS2,CTNNB1,TCF7L2,PRKAR1A
PTEN Signaling	PIK3CA,NRAS,FGFR1,HRAS,FGFR2,KRAS,CCND1,PTEN,BCL2,FGFR3,MAGI1,CBL,AKT1,PDGFRA,KDR,EGFR
Role of Tissue Factor in Cancer	TP53,SRC,PIK3CA,NRAS,GNA11,GNAQ,HRAS,KRAS,JAK2,PTEN,F10,AKT1,PTPN11,ITGB5,EGFR,ATM
VEGF Family Ligand-Receptor Interactions	PIK3CA,AKT1,NRAS,HRAS,KRAS,KDR,ATM
VEGF Signaling	SRC,PIK3CA,AKT1,NRAS,PTPN11,HRAS,KRAS,KDR,ATM,BCL2
Wnt/β-catenin Signaling	TP53,CDKN2A,SRC,GNAQ,CCND1,HNF1A,APC,ACVR1B,MYC,CDH1,PPP2R1A,AKT1,DKK3,SMO,CTNNB1,TCF7L2

13.5 APPENDIX E: COLLECTION/RECORDING OF BLOOD PRESSURE INFORMATION

1.0 General Guidelines

1.1 Frequency of monitoring. Blood pressure (BP) should be monitored at baseline, and then at every clinic visit, as well as at home during weeks when there is no clinic visit.

1.2 Data recording. All required data should be recorded in the appropriate CRF or on the patient's blood pressure monitoring diary, as appropriate. **The following data are required at baseline and at each subsequent assessment**:

- Assessment date and time
- Pulse
- Systolic and diastolic BP

1.3 Risk factors for hypertension (assess and record data in baseline history/physical CRF)

- Diabetes (type 1 or type 2)
- Renal disease (specify on CRF)
- Endocrine condition associated with HTN (specify on CRF)
- Use of steroids or NSAIDs (specify all concomitant meds)
- Underlying cardiovascular condition – specify (*i.e.*, ischemic heart disease)

2.0 Baseline data collection (at study entry)

2.1 All patients

- Current BP
- Proteinuria, if present

2.2 Patients with preexisting hypertension (*i.e.*, those for whom "hypertension" is entered as a concomitant condition at study entry, or those who are currently receiving therapy with antihypertensive medication) – also record:

- Date of HTN diagnosis (original)
- Type HTN (essential or secondary)
- CTCAE grade of HTN (at time of study entry)
- Trade name, drug class*, dose, dose frequency, start/stop dates/ongoing of the following:
  - Antihypertensive agents taken at study entry
  - Antihypertensive agents taken in past (e.g., discontinued for toxicity, lack of efficacy)

3.0 Follow up BP data collection (during study)

3.1 All patients (at each clinic visit)

- Current BP
- Proteinuria, if present

3.2 Patients with treatment-emergent hypertension [defined as BP increase of >20 mmHg (diastolic) OR systolic BP >139 OR diastolic BP > 90 (if previously normal or grade 1 per CTCAE v4) – record at time of hypertension diagnosis and at all subsequent clinic visits:

- BP changes from baseline (or from previous assessment) (specify CTCAE

grade changes)
- Hypertension-related symptoms as reported by patient (*e.g.*, headache)
- Other relevant changes associated with development of hypertension (*e.g.*, ECG abnormalities)
- Trade name, drug class*, dose, dose frequency, start/stop dates/ongoing of currently prescribed antihypertensive agents

3.3 Patients with pre-existing hypertension at study entry – record at each clinic visit
- BP changes from previous clinic visit (specify CTCAE grade changes)
- Hypertension-related symptoms reported by patient (*e.g.*, headache)
- Other relevant changes associated with development of hypertension (*e.g.*, ECG abnormalities)
- Changes in antihypertensive medications since last assessment (*e.g.*, dose change, add/discontinue drug)

*Classes of antihypertensive drugs include ACE inhibitors, calcium channel blockers, alpha blockers, beta blockers, diuretics, angiotension II receptor antagonists.

13.6 APPENDIX F: PATIENT DRUG ADMINISTRATION DIARY

13.6.1 Sunitinib

Patient Name _____ Study ID _____

Please complete this form and return to the research nurse or doctor every cycle

You will take: Sunitinib **Dose**: _____ mg each morning with or without food. Be advised to drink plenty of water while you are on sunitinib.

You will only need to take your blood pressure once per week. Please be sure you are seated when you take the measurement.

DAY	DATE	TIME TAKEN	Blood Pressure	COMMENTS (side effects or missed doses)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				

27				
28				

13.6.2 Everolimus

Patient Name _____ Study ID _____

Please complete this form and return to the research nurse or doctor every cycle

You will take: E**verolimus** Dose: _____.

DAY	DATE	TIME TAKEN	COMMENTS (side effects or missed doses)
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
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25			
26			
27			
28			

Patient Signature:_____

13.7 APPENDIX G: CHILD PUGH SCORE

Parameter	1 point	2 points	3 points
Total bilirubin (mg/dl)	<2	2-3	>3
Serum albumin, (g/dl)	>3.5	2.8-3.5	<2.8
PT INR	<1.7	1.71-2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points are assigned based on the above parameters and totaled. Based on totals the following categories are assigned.

Points	Child Pugh Class
5-6	A
7-9	B
10-15	C