A phase I/II study of X-82, an oral anti-VEGFR tyrosine kinase inhibitor, with everolimus for patients with pancreatic neuroendocrine tumors

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Principal Investigator Signature Page

Principal Investigator:	Benjamin R. Tan, M.D.	
	Signature of Investigator	Date
	Printed Name of Investigator	
	By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.	

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SCHEMA

Phase I

Dose Escalation Schedule		
Dose Level	**X-82 Dose**	**Everolimus Dose**
Level -1	50 mg QD	10 mg QD
Level 0 (Starting Dose)	100 mg QD	10 mg QD
Level 1	150 mg QD	10 mg QD
Level 2	200 mg QD	10 mg QD
Level 3	300 mg QD	10 mg QD
Level 4	400 mg QD	10 mg QD

Note: Enrollment to Phase II and the PK Expansion Cohort will take place simultaneously.

Phase II

X-82 will be given orally once daily at the recommended phase II dose. Everolimus 10 mg will be given orally once daily. These patients will be randomized to one of two groups: the first group will begin taking everolimus 3 weeks prior to initiating X-82, while the second group will begin taking X-82 3 weeks prior to initiating everolimus. Cycle 1 Day 1 will be considered the day when both study drugs are taken together for the first time. The lead-in period will be referred to as Cycle 0.

PK Expansion Cohort for Renal Cell Carcinoma

X-82 will be given orally once daily at the recommended phase II dose. Everolimus 10 mg will be given orally once daily. Three evaluable patients with renal cell carcinoma will be enrolled to each of the following groups:

Group A: Will take everolimus first, followed by X-82 two hours later
Group B: Will take everolimus first, followed by X-82 four hours later
Group C: Will take X-82 and everolimus at the same time

Blood will be drawn for pharmacokinetic testing on Cycle 1 Day 14.

Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
AUC	Area under the curve
BP	Blood pressure
CBC	Complete blood count
CFR	Code of Federal Regulations
CMP	Complete metabolic panel
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCE-MRI	Dynamic contrast enhanced-magnetic resonance imaging
DLTs	Dose Limiting Toxicities
DNA	Deoxyribonucleic acid
DOB	Date of birth
DSM	Data and Safety Monitoring
ECG (or EKG)	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FWA	Federal wide assurance
G-CSF	Granulocyte colony stimulating factor, filgrastim (Neupogen)
GI	Gastrointestinal
GPS@WU	Genomic and Pathology Services at Washington University
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HHS	Department of Health and Human Services'
HIV	Human immunodeficiency virus
HRPO	Human Research Protection Office (IRB)
HTN	Hypertension
IND	Investigational New Drug
IRB	Institutional Review Board
LD	Longest diameter
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging

MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
NCCN	National Cancer Center Network
NCI	National Cancer Institute
NET	Neuroendocrine tumor
NIH	National Institutes of Health
NSE	Neuron-specific enolase
NYHA	New York Heart Association
OHRP	Office of Human Research Protections
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PI	Principal investigator
PIGF	Placental growth factor
PNET	Pancreatic neuroendocrine tumors
PO	Per os (orally)
PR	Partial response
PTEN	Phosphatase and tensin homolog
QASMC	Quality Assurance and Safety Monitoring Committee
QD	Quaque die (every day)
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
RNA	Ribonucleic acid
RR	Response rate
SAE	Serious adverse event
SCC	Siteman Cancer Center
SD	Stable disease
TKI	Tyrosine kinase inhibitor
TTP	Time to progression
ULN	Upper limit of normal
UPC	Urine protein to creatinine ratio
UPN	Unique patient number
VEGF	Vascular endothelial growth factor
WBC	White blood cell (count)
WHO	World Health Organization
WU-CaMP	Washington University Cancer Mutational Profile

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1.0 BACKGROUND AND RATIONALE

1.1 Neuroendocrine Tumors

Neuroendocrine tumors (NETs) consist of a spectrum of malignancies arising from neuroendocrine cells in the body, the most common of which are carcinoid tumors and pancreatic neuroendocrine tumors. Carcinoid tumors most commonly arise in the gastrointestinal tract or the lungs or thymus[1]. Median survival for patients with carcinoid is 75 months. Well (G1) to moderately differentiated (G2) carcinoid tumors are associated with a much longer survival (124 and 64 months) compared to those with poorly differentiated (G3) or anaplastic (G4) types (10 months). Pancreatic neuroendocrine tumors (PNETs) represent 1-2% of all pancreatic neoplasms with an estimated incidence of 1 in 100,000[2]. Clinically divided into functional or non-functional groups, NETs are generally classified by the World Health Organization as well differentiated tumor, well differentiated carcinoma or poorly differentiated carcinoma with 5- and 10-year survival rates of 64% and 44%, respectively[3].

1.2 Tyrosine kinase inhibition and NETs

Several reports have shown that vascular endothelial growth factor (VEGF) is key in the angiogenesis, carcinogenesis, and development of resistance in NETs[4-6]. VEGFR2 and VEGFR3 as well as PDGFR are highly expressed in pancreatic neuroendocrine tumor cells[6, 7]. Bevacizumab, an anti-VEGF ligand antibody, resulted in an 18% response rate for patients with NET[8]. Multi-targeted tyrosine kinase inhibitors have also been evaluated for NET. A multi-institutional Phase II study involving 66 patients with advanced PNET and 41 patients with advanced carcinoid noted an overall response rate of 16.7% response in PNET patients and 2.4% for carcinoid patients[9]. Recently, sunitinib, an oral multi-target tyrosine kinase inhibitor, was approved by the Food and Drug Administration (FDA) for the treatment of patients with advanced unresectable pancreatic neuroendocrine tumors. Patients treated with sunitinib had a significantly longer median progression-free survival (PFS) duration of 11.4 months compared to 5.5 months for patients treated with placebo[10]. Response rate is only 9.3%. Approximately 17% of patients on sunitinib discontinued study treatment due to adverse events, including fatigue, diarrhea and congestive heart failure, compared to 8% in the placebo group. Overall survival between the two groups was similar. Another tyrosine kinase inhibitor, sorafenib, has also been evaluated in patients with neuroendocrine tumors[11]. Reported response rates were 11% among 43 patients with PNET and 7% among the 50 carcinoid patients.

1.3 mTOR inhibition and NETs

The mammalian target of rapamycin (mTOR) is a serine-threonine kinase which regulates cell growth, proliferation, and apoptosis through the modulation of the cell cycle[12]. Exome sequencing and expression profiling of well differentiated PNET demonstrated that the mTOR pathway is frequently altered in this malignancy[13, 14]. Activation of the mTOR pathway via the insulin-like growth factor 1 leads to proliferation of neuroendocrine tumor

cells[15]. Rapamycin, an mTOR inhibitor, inhibited carcinoid tumor cell growth in vitro[16]. Temsirolimus has been evaluated in patients with neuroendocrine tumors with an-intent-to treat response rate of 5.6%[17]. Outcomes were similar between patients with carcinoid tumors and pancreatic neuroendocrine tumors. Another phase II study treated 30 patients with carcinoid and 30 patients with PNET with everolimus with octreotide[18]. Carcinoid patients had a 17% response rate while PNET patients had a 27% response rate to everolimus. The FDA approved the use of everolimus for patients with progressive PNETs based on a randomized Phase III study. A total of 410 patients with low to intermediate grade PNET were treated with either everolimus plus octreotide or placebo + octreotide. Progression free survival was significantly longer among patients treated with everolimus compared to those treated with placebo in the RADIANT-3 study (11 months v 4.6 months, $p<0.001$)[19]. The response rate with everolimus was only 5%. Toxicities included stomatitis, hyperglycemia and, rarely, pneumonitis, among others. Another randomized Phase III study for patients with carcinoid tumors was also conducted (RADIANT2) involving 429 patients. Compared to patients treated with placebo and octreotide, patients treated with everolimus plus octreotide improved PFS from 11.3 months to 16.4 months (hazard ratio 0.77, one sided $p= 0.026$)[20]. Adverse events were minimal and consisted mainly of stomatitis, rash and fatigue.

1.4 X-82

X-82 is an oral multikinase inhibitor targeting VEGFR and PDGFR. Due to its smaller volume of distribution, shorter half-life (approximately 4 to 8 hrs) and limited tissue accumulation, X-82 could potentially minimize toxicities associated with other multikinase inhibitors such as sunitinib and sorafenib while still maintaining targeted efficacy. In a Phase 1 study, no dose limiting toxicities were noted at the 200 mg BID dose level with the capsules[21]. Most toxicities were grade 1 or 2, the most common of which included fatigue, nausea/vomiting, diarrhea and hypertension. One patient developed grade 3 pancreatitis which resolved after discontinuation of drug. One patient with pancreatic cancer had a complete response to therapy while 2 patients with carcinoid tumor had prolonged stable disease beyond 24 weeks.

The current risk profile for X-82 is based primarily on safety data collected from completed nonclinical studies and available literature from similar products, including sunitinib (Sutent®), sorafenib (Nexavar®) and pazopanib (Votrient®); limited information is available to date based on clinical experience with X-82.

The pathology findings from the toxicology studies for X-82 include adrenal cortical changes, lymphoid depletion, pancreatic changes, and bone marrow hypocellularity. Laboratory findings include changes in red blood cell counts, hemoglobin and hematocrit, lower white blood cell and absolute lymphocyte counts and calcium, and higher platelet counts, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, creatine kinase, and potassium.

The toxicity studies also indicate increased toxicities in female rats compared with male rats, likely related to increased drug exposure. These findings were not observed in dogs.

A phototoxicity study in guinea pigs demonstrated sensitivity to light when exposed to X-82.

Approved TKIs have a well characterized adverse event profile. The cardiotoxic effects include a high incidence of hypertension, less frequent occurrence of impaired cardiac function (decreased left ventricular ejection fraction (LVEF) or congestive heart failure), QT prolongation/Torsades de Pointes and cardiac ischemia/infarction. Other warnings or precautions include hepatotoxic effects, including liver failure, thyroid dysfunction, hemorrhage and thrombosis/thrombotic events, hand foot syndrome, gastrointestinal perforation, and proteinuria.

The most common adverse reactions (>20%) noted in at least one of the labels for the approved TKIs are fatigue, asthenia, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, anorexia, weight loss, abdominal pain, constipation, hypertension, peripheral edema, rash/desquamation, hand-foot syndrome, skin discoloration, dry skin, hair color changes, alopecia, altered taste, headache, back ache, arthralgia, extremity pain, cough, dyspnea, and bleeding.

The extent to which adverse events associated with related compounds or the non-clinical toxicology findings noted with X-82 will be observed in the clinical trials is unknown.

1.5 Study Rationale

Targeting both VEGFR and mTOR pathways in neuroendocrine tumors appear to be a reasonable treatment strategy. A recent abstract from the Mayo Clinic Consortium P2C study reported the interim analysis of the Phase II study combining bevacizumab, a VEGF inhibitor, and temsirolimus, an mTOR inhibitor[22]. Confirmed responses were noted in 52% of the first 25 patients enrolled. Progression-free survival at 6 months was 84%. Another study by Yao et al confirmed a 32% decreased tumor blood flow assessed by a CT perfusion scan in pancreatic neuroendocrine tumors treated with bevacizumab[23]. The addition of everolimus to bevacizumab further decreased blood flow by another 15%. There were 26% of patients treated with this combination achieving PRs and 69% of patients with stable disease. Partial responses were associated with decreased tumor blood flow. The Alliance Cooperative group recently completed accrual for the Phase III study randomizing patients with pancreatic neuroendocrine tumors to everolimus alone or with bevacizumab.

When a multi-targeted TK inhibitor, sunitinib was combined with everolimus in a Phase I study for patients with renal cell carcinoma, daily doses of everolimus above 2.5 mg and sunitinib above 37.5 mg were not tolerated[24]. Dose limiting toxicities for sunitinib combined with everolimus included mucositis, thrombocytopenia, febrile neutropenia, vomiting, pulmonary embolism and gastrointestinal hemorrhage. The drug X-82 may be a more tolerable oral multikinase inhibitor with which an mTOR inhibitor such as everolimus could be combined. We therefore propose a Phase I/II study to determine the dose limiting toxicities and the maximum tolerated dose of X-82 in combination with everolimus. The Phase I portion will be conducted in patients with solid tumors and will evaluate the dose

limiting toxicities and determine an appropriate dose of X-82 when combined with everolimus to be used in the Phase II portion. The Phase II portion of the study will assess the response rate and PFS for this combination among patients with pancreatic neuroendocrine tumors.

1.6 Correlative Studies Background

In patients with neuroendocrine tumors, serum chromogranin A and 24-hour urine 5 hydroxyindoleacetic acid (5"-HIAA) level have been routinely measured to assess treatment response. Chromogranin A presents in the chromaffin granules of the neuroendocrine cells, and often becomes detectable in the plasma of patients with neuroendocrine tumors. Worse clinical outcomes are seen in patients with neuroendocrine tumors who have elevated baseline chromogranin A level[25]. Furthermore, declining chromogranin A was found to be predictive of treatment response[26, 27]. For example, based on a phase II study of oral everolimus in patients after failure of cytotoxic therapy, patients with early response of chromogranin A had a longer PFS compared with patients without an early response (13.3 months vs. 7.5 months; HR=0.25; p=0.00004)[26] . In addition, neuron-specific enolase (NSE) has also been shown to be a prognostic marker in PNET[28] . Therefore, we propose to explore the prognostic and predictive value of chromogranin A and NSE in this study.

The mTOR acts in downstream activation of PI3K/Akt, and it plays a key role in the signaling of malignant cell growth, proliferation, differentiation, migration, and survival [29]. Everolimus is an mTOR inhibitor that has FDA approval in patients with PNET[19]. A recent study reported that PIK3CA mutation or phosphatase and tensin homolog (PTEN) loss are linked to sensitivity to mTOR inhibition, but concurrent presence of either KRAS or BRAF mutation renders them treatment resistant[30] . Therefore, we propose to evaluate the predictive significance of a panel of biomarkers including PIK3CA mutation, PTEN loss, KRAS mutation, and BRAF mutation in this trial.

X-82 is an oral multikinase inhibitor mainly targeting VEGFR and PDGFR. Preclinical evidence demonstrates the key role of VEGF in neuroendocrine tumors[31, 32] ; moreover, the clinical benefit of sunitinib further proves the success of anti-angiogenesis strategy in PNET[10]. At present, there have not been validated biomarkers that can predict response to angiogenesis inhibitors. Interestingly, a recent study reported that patients with neuroendocrine tumors with higher serum level of placental growth factor (PIGF), a VEGF homolog, have shorter time to progression (TTP) compared with patients with lower PIGF[33] . In our study, we plan to explore the prognostic and predictive values of serum levels of PIGF along with other angiogenesis biomarkers such as angiopoietin-2, VEGF, FGF et al.

Dynamic contrast enhanced (DCE)-MRI is a non-invasive imaging technique with potential to provide predictive or prognostic information for tumor response[65]. DCE-MRI can be incorporated into clinical MRI examinations to quantitatively evaluate the passage and distribution of gadolinium contrast agents from the circulation to tumors over time. Quantitative perfusion parameters obtained from DCE-MRI were initially applied in the brain and for evaluation for antiangiogenic therapy in cancer treatment[66, 67], but its use has

expanded to other cytotoxic agents and organs[68]. There is growing consensus[69] on which perfusion parameters should be used during the application of DCE-MRI: the transfer constant, K^{trans}, describing the passage of gadolinium from the vascular space to the extravascular, extracellular space[70], and the blood normalized Initial Area under the Gadolinium Curve (IAUGC)[71].

2.0 OBJECTIVES

2.1 Primary Objectives

1. To determine the dose-limiting toxicities and assess the overall toxicities of X-82 in combination with everolimus in patients with solid malignancies (Phase I).

2. To determine the recommended phase II dose for this combination (Phase I).

3. To determine the objective response rate (complete response + partial response) for X-82 in combination with everolimus in patients with pancreatic neuroendocrine tumors (PNETs) (Phase II).

2.2 Secondary Objectives (Phase II)

1. To determine the disease stabilization rate of X-82 in combination with everolimus in patients with PNETs. Disease stabilization rate is defined as the proportion of patients achieving a best overall response of complete response, partial response, or stable disease.

2. To describe the PFS for patients with PNETs treated with X-82 in combination with everolimus.

3. To assess the toxicities of this combination for patients with PNETs.

4. To describe the 3-year overall survival rate of patients with PNET treated with this combination.

5. To evaluate the value of dynamic contrast enhanced (DCE) MRI perfusion parameters as biomarkers of tumor response before and during the first course of treatment with X-82 in combination with everolimus.

2.3 Exploratory Objectives

1. To determine the trough levels of everolimus when administered at the recommended dose of 10 mg daily when combined with X-82.

2. To determine the trough levels of X-82 when combined with everolimus.

3. To determine chromogranin A levels and NSE as prognostic and predictive markers for response to the combination of everolimus and X-82 (Phase II).

4. To assess the predictive values of genetic alterations such as PI3KCA, PTEN, KRAS, and BRAF (Phase II).

5. To analyze the pharmacokinetics of X-82 and everolimus as relating to timing of administration in patients with renal cell carcinoma (PK Expansion Cohort).

3.0 PATIENT SELECTION

3.1 Phase I and PK Expansion Cohort Eligibility

3.1.1 Inclusion Criteria

1. Phase I Patients: Histologic documentation of a solid malignancy and who have exhausted available standard medical treatments or for whom no standard treatments are currently available. This includes primary brain tumors.

2. PK Expansion Patients: Histologic documentation of locally unresectable or metastatic renal cell carcinoma not currently amenable to surgery, radiation, or other therapy with curative intent.

3. Measurable or nonmeasurable disease per RECIST 1.1 criteria.

4. ECOG performance status of 0-1 (see Appendix A).

5. At least 18 years of age.

6. Normal bone marrow and organ function as defined below:
   a. Granulocytes $\geq$ 1,500/mcL
   b. Platelets $\geq$ 100,000/mcL
   c. Hemoglobin $\geq$9 g/dL
   d. Creatinine $\leq$ 1.5 x ULN
   e. Bilirubin $\leq$ 1.5 x ULN
   f. AST and ALT $\leq$ 2.5 x ULN ($\leq$ 5 x ULN if liver metastases are present)
   g. Urine protein $\leq$ 1+ OR urine protein to creatinine ratio $\leq$ 1; if UPC ratio is > 1 on urinalysis, then 24-hour urine collection for protein must be obtained and level must be < 1,000 mg for patient enrollment. (See Appendix B.)

7. QTcF < 450 ms.

8. Normal LVEF.

9. Recovery from any major or minor surgeries.

10. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

11. Ability to swallow and retain oral medication.

12. Able to understand and willing to sign written informed consent document.

3.1.2 Exclusion Criteria

1. Active or severe liver disease (acute or chronic hepatitis, cirrhosis).

2. Patients currently receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization).

3. Receiving any other investigational agent(s) within 21 days or 5 half-lives (whichever is shorter) prior to the first dose of study drug. A minimum of 10 days between termination of the investigational drug and administration of study drug is required.

4. Any radiotherapy or immunotherapy within the last 3 weeks (limited palliative radiation is allowed ≥2 weeks). Chemotherapy regimens with delayed toxicity within the last 4 weeks (or within the last 6 weeks for prior nitrosourea or mitomycin C). Chemotherapy regimens given continuously or on a weekly basis with limited potential for delayed toxicity within the last 2 weeks.

5. Major surgery within the last 4 weeks; minor surgery within the last 2 weeks.

6. Immunization with any attenuated live vaccine within 1 week prior to registration.

7. Concurrent condition resulting in immune compromise, including chronic treatment with corticosteroids or other immunosuppressive agents.

8. History of allergic reactions attributed to, or intolerance of, or other significant toxicity with, compounds of similar chemical or biologic composition to X-82 or everolimus.

9. Patients with fasting serum cholesterol > 300 mg/dL OR > 7.75 mmol/L AND fasting triglycerides > 2.5 x ULN who would need to initiate lipid lowering medications.

10. Concomitant use of drugs with a risk of causing prolonged QTc and/or Torsades de Pointes, or patients with a history of risk factors for Torsades de Pointes (e.g., familial long QT syndrome, heart failure, left ventricular hypertrophy, slow heart rate (<45 beats per minute)).

11. Concomitant use of herbal medications (i.e. St. John's wort, Kava, ephedra (ma huang), ginkgo biloba) at least 7 days prior to the first dose of study drug and throughout participation in the trial.

12. Concomitant use of any drug which is a moderate or strong CYP3A4 inhibitor or strong CYP3A4 inducer.

13. Patients with known CNS metastases, unless metastases are treated and stable and the patients do not require systemic steroids.

14. Treatment with therapeutic doses of coumarin-type anticoagulants (maximum daily dose of 1 mg allowed for port line patency permitted). Low molecular weight heparin (LMWH) will be allowed.

15. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, inadequately controlled hypertension, uncontrolled diabetes mellitus, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or cerebrovascular accident or transient ischemic attack within 6 months of starting study drugs, or psychiatric illness/social situations that would limit compliance with study requirements.

16. Presence of active gastrointestinal (GI) disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of the study drugs.

17. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol.

18. Pregnant or breastfeeding.

19. Known HIV-positivity on combination antiretroviral because of the potential for pharmacokinetic interactions with X-82 or everolimus. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.2 Phase II Eligibility

3.2.1 Inclusion Criteria

1. Histologic documentation of well differentiated or moderately differentiated locally unresectable or metastatic pancreatic neuroendocrine tumor from either a primary or metastatic site with documented disease progression ≤ 12 months prior to enrollment with whose disease is not currently amenable to surgery, radiation or modality therapy with curative intent. If different histologic classification schemes are used, equivalent histologic classifications (for example "grade 1," "low grade," or "intermediate grade") are allowed. There must be histologic documentation of a pancreatic primary site or clinical evidence of a pancreatic neuroendocrine primary tumor as determined by the treating physician. Documentation from a metastatic site is sufficient if there is clinical evidence of a pancreatic primary site. In the case of discordant pathology, patient eligibility will be determined by the PI after review of available records. Patients with neuroendocrine tumors (e.g., gastrinoma, VIPoma) in whom a pancreatic or peripancreatic primary site is strongly suspected are also eligible.

2. Evidence of measurable disease per RECIST 1.1. Measurable disease is defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$ 2 cm with conventional techniques or as $\geq$ 1 cm with spiral CT scan.

3. There is no limit on the number of prior chemotherapy regimens allowed. Any prior treatment (with the exception of lanreotide or octreotide) must be completed at least 4 weeks prior to initiation of treatment. (See exclusion criterion #6.)

4. Prior treatment with embolization or ablative therapies is allowed if measurable disease remains outside of the treated area or if there is definite progression of the treated lesions. There is no limit on the number of prior procedures.

5. ECOG performance status of 0-1 (see Appendix A).

6. At least 18 years of age.

7. Normal bone marrow and organ function as defined below:
   a. Granulocytes $\geq$ 1,500/mcL
   b. Platelets $\geq$ 100,000/mcL
   c. Hemoglobin ≥9 g/dL
   d. Creatinine $\leq$ 1.5 x ULN
   e. Bilirubin $\leq$ 1.5 x ULN
   f. ALT and AST $\leq$ 2.5 x ULN ($\leq$ 5 x ULN if liver metastases are present)
   g. Urine protein $\leq$ 1+ OR urine protein to creatinine ratio $\leq$ 1; if UPC ratio is > 1 on urinalysis, then 24-hour urine collection for protein must be obtained and level must be < 1,000 mg for patient enrollment. (See Appendix B.)

8. QTcF < 450 ms.

9. Normal LVEF.

10. Patients with fasting serum cholesterol > 300 mg/dL OR > 7.75 mmol/L AND fasting triglycerides > 2.5 x ULN should initiate lipid lowering medications.

11. Recovery from any major or minor surgeries. Patient must be 4 weeks post-major surgery and 2 weeks post-minor surgery.

12. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

13. Ability to swallow and retain oral medication.

14. Able to understand and willing to sign written informed consent document.

3.2.2 Exclusion Criteria

1. Poorly differentiated neuroendocrine carcinoma or small cell carcinoma.

2. Prior treatment with everolimus, other mTOR inhibitors, or anti-VEGF drug (sunitinib, bevacizumab).

3. Patients currently receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization).

4. Major surgery < 4 weeks from the start of treatment.

5. Minor surgery < 2 weeks from the start of treatment. (Insertion of a vascular access device is not considered major or minor surgery.)

6. Any radiotherapy or immunotherapy within the last 21 days (limited palliative radiation is allowed ≥2 weeks). Chemotherapy regimens with delayed toxicity within the last 4 weeks. Chemotherapy regimens given continuously or on a weekly basis with limited potential for delayed toxicity within the last 2 weeks.

7. Immunization with any attenuated live vaccine within 1 week prior to registration.

8. Concurrent condition resulting in immune compromise, including chronic treatment with corticosteroids or other immunosuppressive agents.

9. Concomitant use of drugs with a risk of causing prolonged QTc and/or Torsades de Pointes, or patients with a history of risk factors for Torsades de Pointes (e.g., familial long QT syndrome, heart failure, left ventricular hypertrophy, slow heart rate (<45 beats per minute)).

10. Concomitant use of herbal medications (i.e. St. John's wort, Kava, ephedra (ma huang), ginkgo biloba) at least 7 days prior to the first dose of study drug and throughout participation in the trial.

11. Concomitant use of any drug which is a moderate or strong CYP3A4 inhibitor or strong CYP3A4 inducer.

12. Active or severe liver disease (acute or chronic hepatitis, cirrhosis).

13. Positive anti-HBV. HBV seropositive patients (HBsAg positive) are eligible if they are closely monitored for evidence of active HBV infection by HBV DNA testing, and they must agree to receive suppressive therapy with lamivudine or other HBV-suppressive therapy until at least 4 weeks after the last dose of everolimus. Patients who are anti-HCV positive are eligible provided that hepatitis C viral load (hepatitis C RNA) is undetectable.

14. Clinical evidence of brain metastases or carcinomatous meningitis.

15. History of GI perforation within 12 months prior to registration or presence of active gastrointestinal (GI) disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of the study drugs.

16. History of clinically significant bleeding episodes.

17. Current NYHA class II, III, or IV congestive heart failure (see Appendix C) or symptomatic heart failure within 60 days prior to the start of study drugs.

18. Symptomatic arterial peripheral vascular disease.

19. History of aortic aneurysm, aortic dissection, angina, myocardial infarction, stroke, transient ischemic attack, or other arterial thrombotic events within 6 months of registration. Patients on therapeutic non-coumarin anticoagulation are eligible provided that they are on a stable dose of anticoagulants.

20. Uncontrolled diabetes mellitus or inadequately controlled hypertension.

21. Receiving any other investigational agent(s) within 21 days or 5 half-lives (whichever is shorter) prior to the first dose of study drug. A minimum of 10 days between termination of the investigational drug and administration of study drug is required.

22. History of allergic reactions or intolerance of, or other significant toxicity with, attributed to compounds of similar chemical or biologic composition to X-82 or everolimus.

23. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, or psychiatric illness/social situations that would limit compliance with study requirements.

24. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol

25. Pregnant or breastfeeding.

26. Known HIV-positivity on combination antiretroviral because of the potential for pharmacokinetic interactions with X-82 or everolimus. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility by Washington University
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

Once the patient has been entered in the Siteman Cancer Center database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility collecting the information listed below and scanning and emailing it to the research coordinator listed in the *Siteman Cancer Center Clinical Trials Core Protocol Procedures for Secondary Sites* packet at least one business day prior to registering patient:

1. Your name and contact information (telephone number, fax number, and email address)
2. Your site PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Currently approved protocol version date
6. Copy of signed consent form (patient name may be blacked out)
7. Planned date of enrollment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the WUSM research coordinator. Registration will be confirmed by the WUSM research coordinator or by his/her delegate by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through the Siteman Cancer Center database at Washington University.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

4.4 Phase II Randomization

Patients will be randomized in a 1:1 ratio to receive either everolimus three weeks prior to initiating X-82 or X-82 three weeks prior to initiating everolimus. To better ensure the balance of potential risk factors across two groups, the assignment will be done in small blocks of 4 to 6 patients. Randomization will be implemented through the WUSM REDCap (Research Electronic Data Capture). REDCap is a secure, increasingly used web-based application designed exclusively to support data capture for clinical research studies. Specifically, a randomization table will be generated by the study statistician using the SAS program PROC PLAN and uploaded to the WUSM REDCap website. A REDCap account will be created and the study coordinator will be authorized to login for treatment assignment.

5.0 TREATMENT PLAN

5.1 Agent Administration

X-82 is an oral drug which will be administered on an outpatient basis using the dosing schedule in Section 5.3 for patients in phase I and using the recommended phase II dose for patients in phase II and the PK expansion cohort. X-82 will be taken daily on every day of each 28-day cycle. Patients in Levels 0 through 3 should take X-82 at approximately the same time every day; patients in Level 4 should take everolimus first, wait 2 hours, and then take their X-82 dose. Timing of X-82 and everolimus for the PK expansion cohort is described in Section 5.4. If a patient misses a dose, the patient should take the dose as soon as possible, but not less than 12 hours before the next dose is due. If the next dose is due in less than 12 hours, the patient should skip the missed dose and take the next dose as scheduled. If vomiting occurs after taking the study medication, the patient should be instructed not to retake the dose, and should just take his/her next scheduled dose of X-82. Patients will be instructed to bring all unused tablets and their medication diary (see Appendix D) to each study visit for assessment of compliance.

Update as of Amendment #8: The recommended phase II dose was determined to be 300 mg QD due to concerns about the ability to maintain the 400 mg QD dosing level for multiple cycles without significant toxicity

Everolimus is an oral drug which will be administered on an outpatient basis at a dose of 10 mg daily on every day of each 28-day cycle. All patients should take everolimus at the same time as X-82 with the exception of patients enrolled to Level 4 (who should take everolimus first, wait 2 hours and then take X-82) and the PK expansion cohort (See Section 5.4). If a patient misses a dose, the patient should be instructed to take that dose up to 12 hours after the time that s/he would normally take it. If more than 12 hours have elapsed, the patient should skip that dose for the day. Patients should not take 2 doses to make up for the one that was missed. Patients will be instructed to bring all unused tablets and their medication diary (see Appendix E) to each study visit for assessment of compliance.

5.2 Dose Escalation Schema

Dose Level	X-82 Dose	Everolimus Dose
Level -1	50 mg QD	10 mg QD
Level 0 (Starting Dose)	100 mg QD	10 mg QD
Level 1	150 mg QD	10 mg QD
Level 2	200 mg QD	10 mg QD
Level 3	300 mg QD	10 mg QD
Level 4	400 mg QD	10 mg QD

Dose escalation will not occur until all patients in the cohort have completed the first cycle and the Principal Investigator has been able to review all toxicities.

If Level 4 is reached with no DLTs, additional dose escalation cohorts may be added at the discretion of the investigator and the sponsor. Expansion of cohorts (up to 12 patients) at doses lower than MTD may also be undertaken in order to better characterize the safety profile and thereby better define the recommended phase II dose. Once an optimal dose is determined, this will be the recommended phase II dose.

5.3 Phase II Treatment Plan

Once the MTD is determined, additional patients will be enrolled at the recommended phase II dose of X-82 for a goal of 29 evaluable patients. These patients will be randomized to one of two groups: the first group will begin taking everolimus 3 weeks prior to initiating X-82, while the second group will begin taking X-82 3 weeks prior to initiating everolimus (see Section 4.4). Cycle 1 Day 1 will be considered the day when both study drugs are taken together for the first time. The lead-in period will be referred to as Cycle 0. Timing of X-82 and everolimus will depend on which dose level is determined to be the recommended phase II dose. Enrollment to phase II and to the PK Expansion cohort will take place simultaneously.

5.4 PK Expansion Cohort

Once the MTD is determined, three patients with renal cell carcinoma will be enrolled at the recommended phase II dose of X-82 into each the following three groups (nine evaluable patients total):

Group A: Will take everolimus first, followed by X-82 two hours later
Group B: Will take everolimus first, followed by X-82 four hours later
Group C: Will take X-82 and everolimus at the same time

Patients enrolled in the PK expansion cohort will not participate in the lead-in period (Cycle 0) described in Section 5.3).

Blood will be drawn from each patient for pharmacokinetic testing at several time points as described in Section 9.5.

Enrollment to phase II and to the PK Expansion cohort will take place simultaneously.

5.5 Definition of MTD, DLT, Dose Escalation Criteria, and Toxicity, Response, and DLT Evaluations

5.5.1 Definition of Maximum Tolerated Dose (MTD)

The maximum tolerated dose (MTD) is defined as the dose level immediately below the dose level at which 2 patients of a cohort (of 2 to 6 patients) experience dose-limiting toxicity during the first cycle. Dose escalations in the phase I portion of the study will proceed until the MTD has been reached. The recommended phase II dose is the dose to be received during phase II and the PK expansion portion of the study.

5.5.2 Dose Limiting Toxicities (DLTs)

Hematologic DLT is defined as any of the following that occur during the first cycle that are attributed as possibly, probably, or definitely related to the study treatment:

- Grade 4 neutropenia (ANC < 500) > 5 days duration
- Febrile neutropenia of any duration with temperature ≥ 38.5 °C
- Grade 4 thrombocytopenia or grade 3 thrombocytopenia associated with bleeding

Non-hematologic DLT is defined as any possibly, probably, or definitely related grade 3 or grade 4 non-hematologic toxicity that occurs during the first cycle with the following specific exceptions:

- Grade 3 rash if controlled with standard supportive care and lasting ≤ 48 hours
- Grade 3 diarrhea if controlled with standard supportive care and lasting ≤ 48 hours
- Grade 3 nausea if controlled with standard supportive care and lasting ≤ 48 hours
- Grade 3 vomiting if controlled with standard supportive care and lasting ≤ 48 hours
- Grade 3 hypertension if controlled with antihypertensive therapy within 48 hours

Treatment delay of > 14 days due to unresolved toxicity will also be considered a DLT.

5.5.3 Dose Escalation Criteria

Dose escalations will proceed as follows

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. If 0 of these additional patients experience DLT, proceed to the next dose level. If 1 or more of this additional group suffer DLT, then dose escalation is stopped. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This or a lower dose is the recommended phase II dose. At least 6 patients must be entered at the recommended phase II dose during the phase I portion of the study.

5.5.4 Toxicity, Response, and DLT Evaluations

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 30-day follow up after the conclusion of treatment or death.

All patients in Phase II are evaluable for disease response, unless they come off study prior to completion of Cycle 3 and have not had any disease assessment.

A patient is evaluable for DLT assessment only if s/he is enrolled in phase I of the trial, and only during Cycle 1 of treatment. If the patient is not able to be treated on Day 1 of Cycle 2, then s/he is still considered in Cycle 1 active treatment and can experience a DLT. Once the patient has been treated in Cycle 2, s/he will no longer be evaluated for DLTs in all subsequent cycles.

In order for a patient in the PK expansion cohort to be considered evaluable for the PK endpoints, s/he must have taken the drugs as mandated by his/her group assignment and must have had blood drawn at each of the time points specified in Section 9.5. If either of these criteria is not met, the patient will be considered inevaluable for the PK endpoints and will be replaced in that cohort. S/he may still be evaluable for disease response and other endpoints.

5.6 General Concomitant Medication and Supportive Care Guidelines

Standard use of octreotide or lanreotide for patients with neuroendocrine tumors is allowed.

Use of erythropoietin replacement or bisphosphonates is considered supportive care and is

permitted if initiated > 2 weeks prior to start of treatment or after the completion of Cycle 1.

Prophylactic G-CSF is prohibited. However, at the discretion of the treating physician, patients may receive therapeutic G-CSF if neutropenia occurs. Therapeutic use of G-CSF should follow standard ASCO guidelines.

Patients are permitted to receive palliative radiation therapy on study at the discretion of the treating physician.

No routine prophylactic antiemetics will be given; however, antiemetics may be administered with nausea and vomiting when they occur, and may be given prophylactically afterwards.

Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the research team. At each visit, the investigator will ask the patient about any new medications s/he is taking or has taken after the start of study drugs.

The following treatments are prohibited while on this study:

- Chronic treatment with systemic steroids (dose > 10 mg daily of methylprednisolone or equivalent) or another immunosuppressive agent. Topical or inhaled corticosteroids are allowed.
- Anticoagulation with coumarin-derivatives will not be permitted. However, a maximum daily dose of 1 mg will be permitted for port line patency. Should a thrombotic event occur while the patient is receiving treatment, the patient may continue on study. Low molecular weight heparin will be allowed.
- Concomitant treatment with any medication which may cause QT prolongation or Torsades de Pointes is not allowed (See Appendix F). If a patient, after study enrollment, requires use of any medication which may cause QT prolongation and/or Torsades de Pointes, the patient must be removed from study.
- Herbal preparations and medications are not permitted throughout the trial. Patients should stop using these herbal medications at least 7 days prior to the first dose of study drug.
- Live vaccines and close contact with those who have received live vaccines are not permitted on study.

The following drugs should be used with caution:
Potent CYP2C9 substrates which have a narrow therapeutic index (see Appendix G) or potent CYP3A4 inhibitors and inducers (see Appendix H) should be avoided. The co-administration of these drugs with X-82 at high doses could result in increases/decreases in exposure of either the study medication or concomitant medication, and could therefore alter the safety and/or efficacy of these drugs. In addition, due to significant increases in exposure of everolimus, co-administration with moderate or strong CYP3A4 inhibitors and strong CYP3A4 inducers should be prohibited (see Appendix H). Alternative therapies should be used whenever available.

5.7 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative serum or urine pregnancy test within 7 days prior to the first dose of X-82.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for 3 months following the last dose of X-82.

If a patient is suspected to be pregnant, X-82 should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 3 months after the last dose of X-82, the investigator must be notified in order to facilitate outcome follow-up.

5.8 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue indefinitely or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.9 Duration of Follow-up

Patients will be followed for toxicity for 30 days following end of therapy, every 12 weeks for disease progression if patients discontinue for a reason other than disease progression, and every 12 weeks for 3 years for survival. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

Any patients who require treatment delay of more than 3 weeks due to treatment-related toxicity will be discontinued from trial treatment unless the treating physician and PI agree that continued treatment at lower doses is in the best interest of the patient.

6.1 X-82 Dose Modifications

Reduce current dose by 100 mg daily for each dose reduction. Lowest dose allowed is 100 mg QD. Doses will not be re-escalated once reduced. Dose reductions will not be allowed during Cycle 1 for patients enrolled in the phase I portion of this study.

6.1.1 Dose Modifications Due to Hematologic Toxicity

If hematologic toxicity occurs, treatment with X-82 should be held (see Table 2), and re-evaluated in at least 1 week. ANC and platelets should be monitored at least weekly until recovery. If ANC and/or platelets do not recover within 3 weeks, the patient will be discontinued from the trial unless the treating physician and PI agree that continued treatment at lower doses is in the best interest of the patient.

Event	**X-82 Dose**
Neutropenia (ANC)	
Grade 4	Hold dose until recovery to ≤ grade 2, then resume X-82 at one lower dose level.
Recurrent grade 4	Hold dose until recovery to ≤ grade 2, then resume X-82 at one lower dose level.
Thrombocytopenia	
Grade 3	Hold dose until improvement to platelets ≥ 75 x 10^9/L • If resolved in ≤ 5 days, then resume without a dose reduction. • If resolved in > 5 days but < 3 weeks, then resume X-82 at one lower dose level.

6.1.2 Dose Modifications Due to Non-Hematologic Toxicities

If a grade 3 non-hematologic toxicity that is expected to be manageable and reversible with dose reduction occurs, treatment with X-82 should be held until the toxicity resolves to ≤ grade 1. If the grade 3 non-hematologic toxicity lasts longer

than 7 days, study drug will be discontinued. Patients with grade 3 non-hematologic toxicity lasting ≤ 7 days that does not resolve to ≤ grade 1 within 3 weeks should also be removed from the trial, unless the treating physician and PI agree that continued treatment at lower doses is in the best interest of the patient. If a grade 4 non-hematologic toxicity occurs, study drug will be discontinued.

Specific Recommendations for Rash, Nausea, Vomiting and Diarrhea:
For patients with grade 3 rash, nausea, vomiting, and/or diarrhea, X-82, should be held and supportive care initiated. If the grade 3 toxicity lasts ≤ 7 days, patients may restart X-82 at a reduced dose when toxicity returns to ≤ grade 1. If the patient has recurrent grade 3 toxicity despite supportive care, the patient will restart X-82 at the next lower dose level once toxicity has resolved to ≤ grade 1.

Specific Recommendations for Liver Function Test Abnormalities:
For patients with grade 3 liver enzyme elevations (AST/ALT), X-82 should be held until the values recover to ≤ grade 1. Patients with an elevation of ALT ≥ 3 x ULN in conjunction with a bilirubin ≥ 2 x ULN may remain in the study if a correctable, non-drug related cause of the liver test evaluations can be documented; otherwise, the patient must be discontinued from the trial.

Specific Recommendations for the Treatment of Hypertension:
Medication recommendations for the treatment of hypertension should be applied based on the patient and clinical status. General recommendations on initial management of hypertension are:

For persistent HTN (recommend initiation of treatment at consistent BP readings of over 140/90) - initiate treatment with an ACE inhibitor (e.g. benazepril, lisonopril), angiotensin II receptor blocker (ARB) (e.g. - losartan), thiazide diuretic (e.g. - HCTZ), or dihydropyrimidine calcium channel blocker (e.g. - amlodipine). Titrate to BP control with dose escalation of the chosen drug, or if additional agents are needed, choose a second agent from the recommended list.

For patients whose HTN is over 160/90, initiation of combination therapy with an ACE inhibitor and dihydropyrimidine calcium channel blocker is recommended.

6.2 Everolimus Dose Modifications

Doses will not be re-escalated once reduced.

No dose reduction below Dose Level -2 is allowed (see Section 6.2.1).

If more than one dose modification applies, use the most stringent (i.e., the greatest dose reduction).

Patients who do not tolerate treatment with lanreotide or octreotide may discontinue lanreotide/octreotide therapy, but may continue with X-82 and everolimus.

6.2.1 Everolimus Dose Levels

Dose Level	Everolimus
0	10 mg daily
-1	5 mg daily
-2	5 mg every other day

6.2.2 Hematologic Toxicities

For ANC <1000/μL, interrupt everolimus until ANC ≥1000/μL, then resume with one dose level reduction of everolimus. If everolimus is interrupted for ≥3 weeks for ANC, discontinue everolimus unless the treating physician and PI agree that continued treatment at lower doses is in the best interest of the patient.

For platelets <50,000/μL, interrupt everolimus until platelets ≥50,000/μL, then resume with one dose level reduction of everolimus. If everolimus is interrupted for ≥ 3 weeks, discontinue everolimus unless the treating physician and PI agree that continued treatment at lower doses is in the best interest of the patient.

6.2.3 Oral Mucositis

For grade ≥ 2 oral mucositis, interrupt everolimus until mucositis improves to ≤ grade 1, then resume everolimus with 1 dose level reduction.

If everolimus is interrupted for mucositis for ≥ 3 weeks, discontinue everolimus unless the treating physician and PI agree that continued treatment at lower doses is in the best interest of the patient.

6.2.4 Hepatotoxicity

Reactivation of hepatitis B in patients already receiving antiviral therapy is defined as an increase of 1 log in HBV DNA over baseline or the appearance of new measurable HBV DNA and ALT > 5 x ULN.

For reactivation of hepatitis B in patients already receiving antiviral therapy, interrupt everolimus until ALT improves to less than or equal to grade 1, and HBV DNA improves to less than or equal to baseline level, and add a second antiviral. When ALT and HBV DNA improve, resume everolimus with one dose level reduction.

Reactivation of hepatitis B in patients not receiving antiviral therapy is defined as new appearance of measurable HBV DNA.

For reactivation of hepatitis B in patients not receiving antiviral therapy, interrupt everolimus until HBV DNA improves to less than or equal to baseline level, and

add lamuvidine (or other HBV-suppressive therapy). When HBV DNA improves, resume everolimus with one dose level reduction.

If everolimus is interrupted for ≥3 weeks, discontinue everolimus unless the treating physician and PI agree that continued treatment at lower doses is in the best interest of the patient.

Reactivation of hepatitis C is defined as ALT > 5 x ULN (in patients with detectable HCV RNA at baseline) or new appearance of detectable HCV RNA (in patients with knowledge of past hepatitis C infection but no detectable HCV RNA at baseline).

For reactivation of hepatitis C in any patient, discontinue everolimus.

Reactivation of hepatitis B or C is considered a grade 3 (or in the case of a life-threatening event, grade 4) event.

6.2.5 Dose Reductions for other Non-Hematologic Toxicities

For other grade 3 or 4 non-hematologic toxicity (except nausea, vomiting, and fatigue) considered at least possibly due to treatment with everolimus, interrupt everolimus until toxicity resolves to ≤ grade 1. If toxicity improves to ≤ grade 1 within 3 weeks, resume treatment with one dose level reduction of everolimus. Standard supportive measures for the treatment of nausea, vomiting, or fatigue are encouraged, at the discretion of the treating physician.

7.0 REGULATORY AND REPORTING REQUIREMENTS

7.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

7.2 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved 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.

7.3 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

7.4 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

7.5 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Local IRB pre-approval of all protocol exceptions must be obtained prior to the event. For secondary sites, the Washington University PI will issue approval of the exception, but it must also be submitted to the local IRB with documentation of approval forwarded to Washington University. HRPO approval is not required for protocol exceptions occurring at secondary sites.

7.6 Reporting to the Human Research Protection Office (HRPO) and the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur

at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

7.7 Reporting Requirements for Secondary Sites

The research team at each secondary site is required to promptly notify the Washington University PI and research coordinator of all reportable events (as described in Section 7.6) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using either an FDA MedWatch form if required or an institutional SAE reporting form if not). A formal written report must be sent to the Washington University PI and research coordinator within **10 working days** of the occurrence of the event or notification of the secondary site's PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines.

7.8 Reporting to Secondary Sites

The Washington University PI (or designee) will notify the research team at each secondary site of all reportable events that have occurred at other sites (as described in Section 7.6) within **10 working days** of the occurrence of the event or notification of the PI of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable.

7.9 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the investigator to report any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences associated with use of the drug (i.e., there is a reasonable possibility that the experience may have been caused by the drug) by telephone or fax no later than **7 calendar days** after initial receipt of the information. A life-threatening adverse experience is defined as any adverse drug experience that places the subject (in the view of the investigator) 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.
- Report any serious, unexpected adverse experiences associated with the use of the drug, as well as results from animal studies that suggest significant clinical risk within **15 calendar days** after initial receipt of this information. A serious adverse drug experience is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:
    - Death
    - A life-threatening adverse drug experience
    - Inpatient hospitalization or prolongation of existing hospitalization
    - A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
    - A congenital anomaly/birth defect
    - Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

  An unexpected adverse drug experience is defined as any adverse drug experience, the specificity or severity of which is not consistent with the current labeling or investigator brochure (or risk information, if an IB is not required or available).

All MedWatch forms will be sent by the investigator or investigator's team to the FDA at the following address or by fax:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
FAX: 1-800-FDA-0178

Secondary sites must submit a completed MedWatch form to the Washington University

PI and research coordinator within **4 calendar days** (for fatal or life-threatening adverse experiences) or **11 calendar days** (for serious, unexpected adverse experiences). The Washington University PI will be responsible for submitting all MedWatch forms from secondary sites to the FDA within the timeframes specified above.

7.10 Reporting to Tyrogenex

Tyrogenex or designee is responsible for reporting relevant SAEs to participating investigators in other trials using X-82, in accordance with ICH guidelines, FDA regulations, and/or local regulatory requirements.

Any death while on study or within 30 days of study or any reportable death (considered possibly related to study drug) more than 30 days after end of study will be reported to Tyrogenex within 24 hours. Any reportable adverse events as described in Sections 7.1 and 7.2 and 7.7 will be reported to Tyrogenex within 24 hours. A safety report will be provided to the Tyrogenex on a monthly basis, including all serious adverse events. All noncompliance and serious noncompliance described in Sections 7.3 and 7.4 will be reported to Tyrogenex within 10 days.

All reports should be sent to the Tyrogenex at the following email address or by fax:

X82-CLI-102@tyrogenex.com
FAX: 1-561-828-0228

7.11 Timeframe for Reporting Required Events

Reportable adverse events will be tracked for 30 days following the last day of study treatment. For the purposes of this study, abnormal lab values will only be considered adverse events if they are clinically significant.

8.0 PHARMACEUTICAL INFORMATION

8.1 X-82

8.1.1 X-82 Description

X-82 is a small molecule indolinone inhibitor of a family of type III and type V receptor tyrosine kinases characterized by an extracellular domain containing several immunoglobulin-like domains, a membrane spanning region, and a cytoplasmic split kinase domain.

Additional information may be found in the X-82 investigator's brochure.

8.1.2 Clinical Pharmacology

Clinical pharmacology studies have not been performed to date.

8.1.3 Supplier(s)

X-82 will be provided free of charge by Tyrogenex.

8.1.4 Dosage Form and Preparation

X-82 will be supplied in 100 mg tablets.

8.1.5 Storage and Stability

X-82 tablets (100 mg) are stored in 60cc wide mouth round HDPE bottles with one Sorbit ½ gram desiccant canister. Thirty tablets are included in each bottle.

X-82 should be stored at room temperature (15ºC-30ºC/59ºF- 86ºF).

8.1.6 Administration

X-82 is an oral tablet intended to be taken at the same time every day. If a patient misses a dose, the patient should take the dose as soon as possible, but not less than 12 hours before the next dose is due. If the next dose is due in less than 12 hours, the patient should skip the missed dose and take the next dose as scheduled. If vomiting occurs after taking the study medication, the patient should be instructed not to retake the dose, and should just take his/her next scheduled dose of X-82.

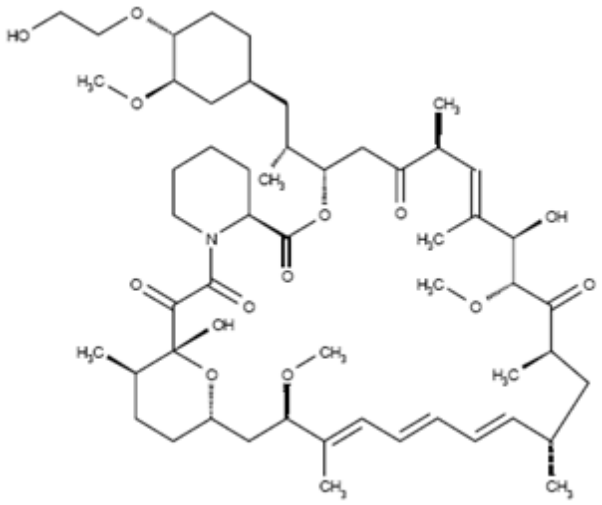
8.2 Everolimus

8.2.1 Everolimus Description

Everolimus, an inhibitor of mTOR, is an antineoplastic agent. It is FDA approved for adults with progressive neuroendocrine tumors of pancreatic origin that are unresectable, locally advanced, or metastatic.

The chemical name of everolimus is (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-dimethoxy15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20pentaone.

The molecular formula is C53H83NO14 and the molecular weight is 958.2. The structural formula is:



8.2.2 Clinical Pharmacology

Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation with mTOR complex 1 (mTORC1) and thus inhibition of mTOR kinase activity. Everolimus reduced the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP1), downstream effectors of mTOR, involved in protein synthesis. S6K1 is a substrate of mTORC1 and phosphorylates the activation domain 1 of the estrogen receptor which results in ligand-independent activation of the receptor. In addition, everolimus inhibited the expression of hypoxia-inducible factor (e.g., HIF-1) and reduced the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in *in vitro* and/or *in vivo* studies.

Constitutive activation of the PI3K/Akt/mTOR pathway can contribute to endocrine resistance in breast cancer. *In vitro* studies show that estrogen-dependent and HER2+ breast cancer cells are sensitive to the inhibitory effects of everolimus, and that combination treatment with everolimus and Akt, HER2, or aromatase inhibitors enhances the anti-tumor activity of everolimus in a synergistic manner.

Two regulators of mTORC1 signaling are the oncogene suppressors tuberin-sclerosis complexes 1 and 2 (*TSC1*, *TSC2*). Loss or inactivation of either *TSC1* or *TSC2* leads to activation of downstream signaling. In TSC, a genetic disorder, inactivating mutations in either the *TSC1* or the *TSC2* gene lead to hamartoma formation throughout the body.

8.2.3 Pharmacokinetics and Drug Metabolism

Absorption
In patients with advanced solid tumors, peak everolimus concentrations are reached 1 to 2 hours after administration of oral doses ranging from 5 mg to 70 mg. Following single doses, Cmax is dose-proportional between 5 mg and 10 mg. At doses of 20 mg and higher, the increase in Cmax is less than dose-proportional, however AUC shows dose-proportionality over the 5 mg to 70 mg dose range. Steady-state was achieved within 2 weeks following once-daily dosing.

Food effect: In healthy subjects, high fat meals reduced systemic exposure to everolimus 10 mg tablet (as measured by AUC) by 22% and the peak blood concentration Cmax by 54%. Light fat meals reduced AUC by 32% and Cmax by 42%. Food, however, had no apparent effect on the post absorption phase concentration-time profile.

Distribution
The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given everolimus 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

Metabolism
Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, everolimus is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus.

These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100-times less activity than everolimus itself.

In vitro, everolimus competitively inhibited the metabolism of CYP3A4 and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan.

Excretion
No specific excretion studies have been undertaken in cancer patients. Following the administration of a 3 mg single dose of radiolabeled everolimus in patients who were receiving cyclosporine, 80% of the radioactivity was recovered from the feces, while 5% was excreted in the urine. The parent substance was not detected in urine or feces. The mean elimination half-life of everolimus is approximately 30 hours.

8.2.4 Supplier(s)

Everolimus is commercially available.

8.2.5 Dosage Form and Preparation

For this study, everolimus will be available commercially at 5 or 10 mg.

8.2.6 Storage and Stability

Store everolimus at room temperature, away from light.

8.2.7 Administration

Everolimus is an oral drug which will be administered on an outpatient basis at a dose of 10 mg daily on every day of each 28-day cycle. Patients should take everolimus at the same time as X-82. If a patient misses a dose, the patient should be instructed to take that dose up to 12 hours after the time that s/he would normally take it. If more than 12 hours have elapsed, the patient should skip that dose for the day. Patients should not take 2 doses to make up for the one that was missed. Patients will be instructed to bring all unused tablets and their medication diary (see Appendix E) to each study visit for assessment of compliance.

8.2.8 Special Handling Instructions

None.

9.0 CORRELATIVE STUDIES

9.1 Archived Tumor Tissue

FFPE samples from previous diagnostic or therapeutic procedures will be requested. Tissue blocks are preferable; however, if the tissue block cannot be obtained, 20 unstained slides sectioned at 5 microns will be required. Archival tumor tissue will be analyzed by the Genomic and Pathology Service at Washington University using the Washington University Cancer Mutational Profile (WU-CaMP), which was designed to perform full gene sequencing on a panel of 28 genes which include PI3KCA, KRAS, BRAF and PTEN. The Wu-CaMP assay subjects DNA extracted from paraffin-embedded tumor specimens or fresh tumor biopsy to next-generation sequencing technology for mutation analysis. Ki-67 proliferation index will be collected as well.

9.2 Tumor Biopsy (Optional)

Fresh tumor biopsy samples will be obtained where feasible by CT or ultrasound-guided

core biopsy. Some areas that are considered feasible are chest wall lesions, skin lesions, palpable lymph nodes, liver lesions, lung lesions, or other areas deemed feasible by the treating physician or study PI. Samples will be obtained at baseline (up to 28 days before Cycle 1 Day 1). These samples will be snap frozen for future comprehensive genomic analysis.

Accrued biopsy samples will be identified through HRPO number and protocol number, patient's entry number, and sample collection date and time, and this information will be securely affixed by means of pre-made labels. Samples will be released for laboratory analysis by specimen ID only.

All biopsy samples will be processed and stored by the Siteman Cancer Center Tissue Bank. The address and contact information are provided below.

Siteman Cancer Center Tissue Procurement Facility
BJC Institute of Health
425 S. Euclid Ave., Room 5120
St. Louis, MO 63110
Phone: 314-454-7615

9.3 Blood Samples

All samples will be taken to Siteman Cancer Center's Tissue Procurement Core (BJCIH 5th fl) after they are drawn. No special processing need take place before delivery. Please use the shipping address in provided in Section 9.2.

9.3.1 Blood for Trough Levels

Blood (10 mL) will be collected in 2 lavender top tubes (5 mL K2 EDTA tubes) on Cycle 2 Day 1 prior to dosing for evaluation of trough levels of everolimus and X-82.

9.3.2 Blood for Chromogranin A, Neuron-specific Enolases (NSE), and Angiogenesis Biomarker (Phase II Only)

Blood (10 mL) will be collected in 1 lavender top tube (5 mL K2 EDTA tube) and 1 red top tube (5 mL) for evaluation of chromogranin A, neuron-specific enolases (NSE), and angiogenesis biomarker. Serum and plasma samples will be collected at the following time points:

- Baseline
- Pre-dose on Day 1 of every cycle beginning with Cycle 2

Please note that if chromogranin A and NSE at baseline are less than upper limit of normal, there will not be further collection of both biomarkers during subsequent cycles.

Evaluation of chromogranin A is a standard care for patients with NETs; therefore, the test will be carried out by the Barnes-Jewish Laboratory. NSE will be analyzed by Quest Diagnostic by using a solid-phase, noncompetitive enzyme immunoassay (Yao et al 2011).

To evaluate the angiogenesis biomarkers, plasma samples will be analyzed by commercially available enzyme linked immunosorbent system (ELISA) kit which will determine the expression levels of a panel of angiogenesis biomarkers including angiopoietin-2, endothelin-1, EGF, FGF, TNFα, HGF, IL-8, Leptin, PIGF, VEGF and HB-EGF.

9.4 DCE-MRI (Phase II Only - Optional)

Patients must have ≥3 cm target lesion in order to be eligible for the DCE-MRI.

The schedule of evaluation with DCE-MRI is as follows:

1. Before initiation of either study drug (baseline)
2. 21 +/- 3 days after initiation of the first study drug (patients will be randomized to one of two groups: one group will begin taking everolimus 3 weeks prior to X-82, and the other group will begin taking X-82 3 weeks prior to everolimus)
3. 21 +/- 3 days after initiation of the second study drug

DCE-MRI will be performed following injection of contrast at a rate of 2 ml/s, with a delay of 6 s, followed by 20 ml of saline flush using an automatic injector. Gadobenate dimeglumine (Gd-BOPTA, MultiHance, Bracco Diagnostics, Inc., Princeton, NJ) will be used at a standard concentration of 0.1 mmol/kg. A series of images will be acquired over a time period of 4-5 min with a temporal resolution of approximately 8 s. Oblique coronal images covering the tumor and including the abdominal aorta will be performed under the guidance of pre-contrast T1 and T2 weighted images. The nominal parameters for the DCE-MRI, 3D spoiled gradient echo sequence (SPGR) are: TE = 1 ms, TR = 4 ms, flip angle 30 degrees, slice thickness 5 mm (with zero-filling), matrix size = 256x128, 12 slices, FOV = 320x320 mm, bandwidth = 23.8 kHz, NEx = 1.0, and number of phases = 30. A 3D SPGR sequence with the same parameters above will be performed for T1 mapping of the liver, using multiple flip angles (e.g., FA = 2, 5, 10, 15, 20, 25, 30 degrees) in the same acquisition plane.

9.5 Blood for Pharmacokinetic Testing (PK Expansion Cohort Only)

2.5 mL of blood will be drawn from patients enrolled in the PK expansion cohort at the following time points on Cycle 1 Day 14:

- Pre-administration of everolimus
- 1 hour post-administration of everolimus
- 2 hours post-administration of everolimus (prior to X-82 dosing for Group A)
- 3 hours post-administration of everolimus

- 4 hours post-administration of everolimus (prior to X-82 dosing for Group B)
- 5 hours post-administration of everolimus (for Groups A and B only)
- 6 hours post-administration of everolimus
- 7 hours post-administration of everolimus (for Group B only)
- 8 hours post-administration of everolimus
- 10 hours post-administration of everolimus (for Groups A and B only)
- 12 hours post-administration of everolimus (for Group B only)

Collect blood sample using one 10 mL lavender-top K2 EDTA collection tube at the time points specified. After obtaining the blood sample, invert the tubes 8 times (process within 30 minutes of blood collection). Centrifuge at 3000rpm for 10 minutes at 4°C temperature in swing-bucket centrifuge. Carefully aspirate plasma supernatant without disturbing the buffy coat layer. Transfer duplicate plasma aliquots of approximately equal volume, using standard laboratory technique, into 2 appropriately-labeled 2 mL cryovial tubes. Ensure that the white labels are completed with pertinent study and patient information and affix one label to each 2mL cryovial tube. Immediately store both plasma aliquot samples in a freezer set to maintain a temperature of -70°C. Complete the shipping manifest electronically with all the required specimen information. A shipping manifest MUST BE sent to Covance prior to shipment to ensure accurate processing of the patient samples. Print two copies of the manifest, one copy to be included in the sample shipment and one copy to be included in the site files. Ship the samples to Covance for analysis:

Attention: Amber LaFayette
Sample Management—Bioanalytical (Rm 1S 160)
Covance Laboratory Inc.
3301 Kinsman Boulevard
Madison, WI 53704-2523

Phone: 608-395-3750

Send the electronic copy of the sample inventory form in .xls format (shipping manifest) to: Madison.SA@covance.com **AND** amber.lafayette@covance.com.

10.0 STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days +/- 2 days prior to start of protocol therapy. Scans and x-rays must be done no more than 28 days +/- 2 days prior to the start of the protocol therapy.

10.1 Phase I and PK Expansion Cohort Study Calendar

	Baseline	Day 1 of each cycle	End of every third cycle	Follow-up[k]
Informed consent	X			
Medical history	X			
Physical exam, incl. weight, PS	X	X		X
CBC[a]	X	X[n]		
CMP[b] (fasting)	X	X[n]		
Fasting serum cholesterol and triglycerides	X		X	
Serum or urine pregnancy test[c]	X			
Urinalysis	X			
Hepatitis B test	X			
EKG	X	X[g]		
Echocardiogram or MUGA[d]	X			
CT or MRI or PET/CT	X[e]		X	
Archival tissue for WU-CaMP assay	X			
OPTIONAL biopsy[e]	X			
Blood for trough levels of everolimus and X-82		X[j]		
Blood for PKs		X[o]		
X-82[f]		X ---------- X		
Everolimus[f]		X ---------- X		
Adverse event assessment	X ---------- X[m]			
Concomitant medications	X ---------- X			

a: CBC parameters are hemoglobin, hematocrit, RBC, WBC, platelets
b: CMP parameters are glucose, calcium, albumin, total protein, sodium, potassium, carbon dioxide, chloride, BUN, creatinine, alkaline phosphatase, ALT/SGPT, AST/SGOT, bilirubin
c: Women of childbearing potential only; must be performed no more than 7 days before first dose of X-82
d: At baseline and thereafter as clinically indicated
e: May take place up to 28 days before C1D1
f: To be taken daily
g: Day 1 of every even-numbered cycle
h: Will not be drawn on C1D1; will be repeated only if above ULN at baseline
j: Drawn on C2D1 only
k: Follow-up to take place every 12 weeks for 3 years.
m: To 30 days after end of therapy; note that abnormal lab values will be considered AEs and will be captured in the CRFs only if they are clinically significant.
n: Labs will also be drawn on C1D15.
o: For patients in the PK expansion cohort only. Drawn on Cycle 1 Day 14. Refer to Section 9.5 for timing.

10.2 Phase II Study Calendar

	Baseline	C0 D1	C0D21 to 28	Day 1 of each cycle	End of every third cycle	Follow-up[m]
Informed consent	X					
Medical history	X					
Physical exam, incl. weight, PS	X			X		X
CBC[a]	X			X		
CMP[b] (fasting)	X			X		
Fasting serum cholesterol and triglycerides	X				X	
Serum or urine pregnancy test[c]	X					
Hepatitis B test	X					
Urinalysis	X					
EKG	X			X[h]		
Echocardiogram or MUGA[d]	X					
CT or MRI or PET/CT	X[f]				X	
OPTIONAL DCE-MRI [e]	X		X	X[e]		
Archival tissue for WU-CaMP assay	X					
OPTIONAL biopsy[f]	X					
Blood for chromogranin A, NSE, and angiogenesis biomarkers	X			X[j]		
Blood for trough levels of everolimus and X-82				X[k]		
X-82[g]		X ---------- X				
Everolimus[g]		X ---------- X				
Adverse event assessment	X ---------- X[n]					
Concomitant medications	X ---------- X					

a: CBC parameters are hemoglobin, hematocrit, RBC, WBC, platelets
b: CMP parameters are glucose, calcium, albumin, total protein, sodium, potassium, carbon dioxide, chloride, BUN, creatinine, alkaline phosphatase, ALT/SGPT, AST/SGOT, bilirubin
c: Women of childbearing potential only; must be performed no more than 7 days before first dose of X-82
d: At baseline and thereafter as clinically indicated
e: DCE-MRI will be performed at baseline, 21 +/- 3 days after initiation of the first study drug (~C0D21), and then again 21 +/- 3 days after initiation of the second study drug (C1D21).
f: May take place up to 28 days before C1D1
g: To be taken daily; patients in Phase II will be randomized so that half begin taking everolimus 3 weeks prior to starting X-82, while the other half begin taking X-82 3 weeks prior to starting everolimus. Please note that Cycle 1 Day 1 is considered to be the first day when both drugs are taken.
h: Day 1 of every even-numbered cycle
j: Will not be drawn on C1D1; will be repeated only if above ULN at baseline
k: Drawn on C2D1 only
m: Follow-up to take place every 12 weeks for 3 years.
n: To 30 days after end of therapy; note that abnormal lab values will be considered AEs and will be captured in the CRFs only if they are clinically significant.

11.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Electronic data management systems will be used in this trial in collaboration with the Center for Biomedical Informatics core at Washington University.

ClinPortal is a web-based clinical studies data management system that will be used for capture of clinical data from this trial. The case report forms developed for this trial will be transformed to electronic format. An electronic study calendar will drive the study's data collection workflow. An Oracle database securely stores PHI in compliance with HIPAA and IRB regulations.

Identical study databases will be created in ClinPortal for each participating center; each center has access only to data from its own participants. Washington University, as the data coordinating center, has access to data from all sites.

Training in entering data in ClinPortal is required before a participating center will be given access to its site's database. The Center for Biomedical Informatics at Washington University offers monthly web-based training for external users; the scheduled may be found at the following URL: http://cbmi.wustl.edu/?q=clinportal-training-details. Users must RSVP at least 3 days prior to the training session.

In addition, a participating center must have IRB approval of this protocol prior to initiation of ClinPortal data entry training, which must be completed prior to study activation.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Registration Form Eligibility Form On-Study Form Tissue Collection Form Research Blood Form Treatment Assignment Form	Prior to starting treatment
Treatment Form Research Blood Form	Every cycle
Toxicity Form Concomitant Medications Form	Continuous
DCE-MRI Form (Phase II only)	Baseline Cycle 0 Day 21 +/- 3 Cycle 1 Day 21 +/- 3
PK Form (PK Expansion Cohort only)	Cycle 1 Day 14
Treatment Summary Form	Completion of treatment
Follow Up Form	Every 12 weeks for 3 years
Tumor Measurement Form	Baseline, end of every third cycle, and end of treatment
MedWatch Form	See Section 7.0 for reporting requirements

Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4-8 weeks (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new 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.

12.2 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 >20 mm by chest

x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (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.

12.3 Methods for Evaluation of Measurable Disease

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

treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: 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. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. 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: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

12.4 Response Criteria

12.4.1 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 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 diameters while on study.

12.4.2 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).

12.4.3 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

12.4.4 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.

12.4.5 Progression-Free Survival

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

12.4.6 Overall Survival

OS is defined as the duration of time from diagnosis to time of death from any cause.

12.4.7 Response Review

Response rate is the primary efficacy endpoint. All responses will be reviewed by an expert(s) independent of the study at the study's completion.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark). The Data and Safety Monitoring Committee (DSMC) will meet to review toxicity data at least every 6 months following the activation of the first secondary site.

During the phase I dose escalation, the Principal Investigator will review all patient data at least monthly (or before each dose-escalation if occurring sooner than monthly), and provide a semi-annual report to the Quality Assurance and Safety Monitoring Committee (QASMC). During the phase II, the Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason

- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date, accrual by site, and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities at all participating sites separated by cohorts with the number of dose-limiting toxicities indicated
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Until such a time as the first secondary site activates this protocol, a semi-annual DSM report to be prepared by the study team will be submitted to the QASM Committee beginning 6 months after study activation at Washington University. The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

A DSMC will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. Like investigators, DSMC members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMC will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMC must also be disclosed.

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMC at http://www.siteman.wustl.edu/uploadedFiles/Research_Programs/Clinical_Research_Resources/Protocol_Review_and_Monitoring_Committee/QASMCQualityAssurcance.pdf

14.0 AUDITING

Since Washington University is the coordinating center, each site will be audited annually by Siteman Cancer Center personnel (QASMC) unless the outside institution has an auditing mechanism in place and can provide a report. The outside sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Additional details regarding the Auditing Policies and procedures can be found at http://www.siteman.wustl.edu/uploadedFiles/Research_Programs/Clinical_Research_Resources/Protocol_Review_and_Monitoring_Committee/QASMCQualityAssurcance.pdf

15.0 STATISTICAL CONSIDERATIONS

15.1 Primary Endpoints and Objectives

The primary objective of the Phase I portion is to determine the dose-limiting toxicities of X-82 in combination with everolimus in patients with solid malignancies and to determine the recommended phase II dose for this combination.

The primary objective of the Phase II portion is to determine the preliminary efficacy (as measured by complete response and partial response) for X-82 in combination with everolimus in patients with pancreatic neuroendocrine tumor.

15.2 Study Design

The Phase I portion will be conducted using a standard 3+3 design. The definition of DLT as well as the procedures of dose escalation have been detailed in Section 5.4. Depending on the dose level identified as the MTD, up to a maximum of 30 subjects may be required to determine the MTD (5 dose levels with a maximum of 6 patients per level) according to the 3+3 design.

A total of 29 evaluable patients will be enrolled for the Phase II portion. The patients enrolled at the recommended phase II dose in the Phase I portion will not be counted as Phase II participants. We assume a null hypothesis of 5% overall response rate. We hypothesize that an overall response rate of 20% or higher warrants further investigation. Based on Simon's optimal two-stage design with 80% power at a 0.05 significance level, 10 patients will be enrolled in the first stage. If 1 or more responses are observed during the first stage, then 19 additional patients will be enrolled in stage II. If 4 or more responses are observed by the end of the trial, we would conclude that preliminary evidence for efficacy exists and that further investigation of the drug is warranted. Note, however, that an assessment of all of the efficacy and biomarker data, not just response rate, will ultimately be used to make this determination. A total of 32 patients will be enrolled assuming 10% of cases will be inevaluable.

Finally, 9 additional patients with renal cell carcinoma will be enrolled to the PK expansion cohort.

15.3 Data Analysis of the Phase II Study

Demographic and clinical characteristics of the sample, as well as response, toxicity by grade, and loss to follow up will be summarized using descriptive statistics. The overall response rate and disease stabilization rate, as well as their 95% confidence intervals, will be calculated. The toxicities by grade will also be tabulated. Kaplan-Meier product limit estimator will be used to describe the distribution of overall survival (OS) and progression-free survival (PFS). The median OS and PFS and their 95% confidence intervals will be estimated.

In the correlative studies, the association between clinical outcomes (response, PFS, and OS) and biomarkers (including chromogranin A, neuron-specific enolase, the mutation status of PIK3CA, PTEN loss, KRAS and BRAF, as well as serum level of PIGF, angiopoietin-2, VEGF, FGF et al.) will be assessed using Wilcoxon-Mann-Whitney rank-sum tests, log-rank tests or univariate Cox proportional hazards models as appropriate.

15.4 DCE-MRI Analyses

The DCE imaging will be evaluated for changes in Ktrans and initial area under the curve, which are parameters reflecting the passage of Gadolinium contrast agent from the vascular space to the extravascular, extracellular space. The kinetic parameters and ADC values will be correlated with objective tumor response based upon RECIST 1.1 guidelines. The tumor measurements will be performed by a reference radiologist using MRI, CT, or PET/CT. Phase II patients will be randomized into two groups: one group will start taking everolimus 3 weeks prior to initiation of X-82, and the other group will start taking X-82 3 weeks prior to initiation of everolimus. Tumor DCE kinetic parameters and ADC measurement will be evaluated at baseline, 21 +/- 3 days after the initiation of the first study drug, and then 21 +/- 3 days after the initiation of the second study drug. The ADC values and kinetic parameters will be correlated with overall survival and progression-free survival once this data is available at the termination of the study.

Changes in tumor perfusion parameters and ADC values through Cycle 1 Day 21 +/- 3 will be correlated with objective response as determined by anatomic measurements on follow-up MRI, CT, or PET/CT using guidelines from RECIST 1.1. Changes in DCE-MRI parameters will be compared between the first and second scan using a signed-rank test. The change of DCE-MRI values over time will be described using two-way ANOVA for repeated measurement data, followed by post-hoc comparisons for between-time or between-group differences of interest. The association between these changes and patient outcome (RECIST response and progression-free survival) will be explored using Cox regression (for PFS) and logistic regression (for response). With at least 29 evaluable patients we will have approximately 80% power at a 1-sided 0.05 significance level to detect changes from baseline that are 50% of the standard deviation of the change score.

16.0 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Each participating institution must have the following documents on file at Washington University prior to first subject enrollment:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
- Documentation of FWA, signed FDA Form 1572, and signed and dated CVs of all participating investigators.
- Documentation of training in protection of human subjects by all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The Principal Investigator is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. There will be one current version of the protocol document at any given time and each participating institution will utilize that document. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 2 weeks of obtaining Washington University IRB approval with acknowledgement of receipt requested. Secondary sites are to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt, and confirmation of submission must be forwarded to the appropriate contact person on the Washington University study team at the time of submission. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

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APPENDIX A: ECOG Performance Status Scale

Grade	Description
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.

APPENDIX B: UPC Ratio Calculation

The UPC (urine protein to creatinine) ratio directly correlates with the grams of protein found in a 24-hour urine collection. The UPC ratio can be used in the place of a 24-hour urine collection.

Procedure for Obtaining a UPC Ratio:

1. Obtain at least 4 mL of a random urine sample in a sterile container (does not have to be a 24-hour urine sample).
2. Determine protein concentration (mg/dL).
3. Determine creatinine concentration (mg/dL).
4. Divide protein concentration by creatinine concentration.

APPENDIX C: NYHA Classification

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs, etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound.

APPENDIX D: Patient's Medication Diary – X-82

Today's Date: _____ Agent: **X-82** Cycle: _____

Patient Name: _____ Study ID#: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month. Take _____mg (___tablets) of X-82 daily at the same time each day. Take it with a glass of water and drink the glass of water in as little time as possible. Swallow the tablets whole and do not chew them. Your doctor will let you know when you should take X-82 relative to everolimus.
2. Record the date, the number of tablets taken, and when you took them.
3. If you forget to take X-82 before 6:00PM, then do not take a dose that day. Restart taking it the next day.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return this form to your physician or study coordinator when you go to your next appointment. Bring your unused study medications and empty bottles with you to each clinic visit so that a pill count can be done.
6. Avoid St. John's Wort or any herbal medications, Seville oranges, grapefruit, grapefruit juice, grapefruit hybrids, pomelos, and exotic citrus fruits from 7 days before you start taking X-82 and throughout the entire study.

Day	Date	What time was dose taken?	# of tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
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28				

APPENDIX E: Patient's Medication Diary – Everolimus

Today's Date: _____ Agent: Everolimus Cycle: _____

Patient Name: _____ Study ID#: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month. Take 10 mg (1 tablet) of everolimus daily at the same time each day. Take it with a glass of water. Your doctor will let you know when you should take everolimus relative to X-82.
2. Record the date, the number of tablets taken, and when you took them.
3. If you forget to take everolimus before 6:00PM, then do not take a dose that day. Restart taking it the next day.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return this form to your physician or study coordinator when you go to your next appointment. Bring your unused study medications and empty bottles with you to each clinic visit so that a pill count can be done.
6. Avoid St. John's Wort or any herbal medications, Seville oranges, grapefruit or its juice or hybrids, pomelos, and exotic citrus fruits from 7 days before you start taking everolimus and throughout the entire study.

Day	Date	What time was dose taken?	# of tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				
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APPENDIX F: Drugs that Prolong QT Interval and/or Induce Torsades De Pointes

This is not a comprehensive list. A complete list may be found and updated at the following web address: http://qtdrugs/org/medical-pros/drug-lists/drug-lists.htm

Antiarrhythmics
Amiodarone
Disopyramide
Dofetilide
Ibutilide
Procainamide
Quinidine
Sotalol

Antibiotics
Clarithromycin
Erythromycin
Gatifloxacin
Moxifloxacin
Sparfloxacin

Antipsychotics
Chlorpromazine
Haloperidol
Mesoridazine
Pimozide
Risperidone
Thioridazine
Ziprasidone

Antidepressants
Amitriptyline
Desipramine
Doxepin
Imipramine
Maprotiline
Venlafaxine

Antifungals
Keotconazole
Itraconazole

Antimalarials
Chloroqine
Halofantrine

Antiemetics
Dolasetron
Domperidone
Droperidol
Ondandsetron
Tropisetron

Miscellaneous
Arsenic trioxide
Bepridil
Methadone
Pentamidine
Cisapride
Tacrolimus

APPENDIX G: CYP2C9 Substrates

The following list describes medications and foods which are common inhibitors, inducers, and substrates of CYP2C9. This list should not be considered all-inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit or induce CYP2C9.

CYP2C9 Substrates

Major	*Minor*
Celecoxib	Amitriptyline
Lmoxicam	Omeprazole
Diclofenac	Miconazole
Ibuprofen	Pitavastatin
Piroxicam	Pheylbutazone
Meloxicam	Rosiglitazone
Phenytoin	Sertraline
Fluvastatin	Sildenafil
Sulfonylurea	Sulfinpyrazone
Glibenclamide	Tamoxifen
Glimepiride	THC
Glipizide	
Tolbutamide	
Irbesartan	
Losartan	
Warfarin	

APPENDIX H: CYP3A4 Moderate and Strong Inhibitors and Strong Inducers

The following list describes medications and foods which are common strong inhibitors of CYP3A4. This list should not be considered all-inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit CYP3A4.

Boceprevir
Conivaptan
Grapefruit juice
Lopinavir
Mibefradil
Posaconazole
Telaprevir
Voriconazole
Ritonavir
Indinavir
Nelfinavir
Saquinavir
Clarithromycin
Telithromycin
Chloramphenicol
Ketoconazole
Itraconazole
Nefazodone
Amprenavir
Aprepitant
Atazanavir
Ciprofloxacin
Darunavir
Diltiazem
Erythromycin
Fluconazole
Fosamprenavir
Imatinib
Verapamil
Avasimibe
Carbamazepine
Phenytoin
Rifampin
St. John's wort