ECOG-ACRIN
cancer research group
Reshaping the future of patient care

E2212

A Randomized, Double-Blinded, Placebo-Controlled Phase II Study of Adjuvant Everolimus Following the Resection of Metastatic Pancreatic Neuroendocrine Tumors to the Liver

STUDY CHAIR:	Steven K. Libutti, M.D.
STUDY CO-CHAIR:	Pamela L. Kunz, M.D.
STUDY STATISTICIAN:	Paul Catalano, Sc.D.
PATHOLOGY CO-CHAIR:	Guang-Yu Yang, M.D., Ph.D.
SURGICAL CO-CHAIR:	Steven K. Libutti, M.D.
LABORATORY STUDIES CO-CHAIR:	Steven K. Libutti, M.D. Luis A. Diaz, M.D.
GASTROINTESTINAL COMMITTEE CO-CHAIRS:	Peter O'Dwyer, M.D. Terence Z. Wong, M.D., Ph.D.

Version Date: April 21, 2014

STUDY PARTICIPANTS
United States Only

Rev. 5/14

ALLIANCE / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology Foundation, Inc
SWOG / SWOG

NOTE: This study is supported by the NCI Cancer Trials Support Unit (CTSU). Institutions not aligned with ECOG-ACRIN will participate through the CTSU mechanism.

ACTIVATION DATE
January 17, 2014

PRE-ACTIVATION DATE
December 23, 2013

Addendum #1 –3/14
Addendum #2 – 5/14
Addendum #3 – 5/14

Agents	IND#	NSC#	Supply	IND Sponsor
Everolimus/Placebo	N/A	NSC 733504	Novartis	IND Exempt

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STUDY CHAIR

Steven K. Libutti, M.D.
Montefiore Medical
3400 Bainbridge Avenue
Map Building, Fourth Floor
Bronx, NY 10467
Phone: 718-920-4231
Fax: 718-798-0309
Email: slibutti@montefiore.org

STUDY CO-CHAIR

Pamela L. Kunz, M.D.
Stanford Cancer Institute
875 Blake Wilbur Drive
Stanford, CA 94305-5826
Phone: 650-725-8738
Fax: 650-498-4696
Email: pkunz@stanford.edu

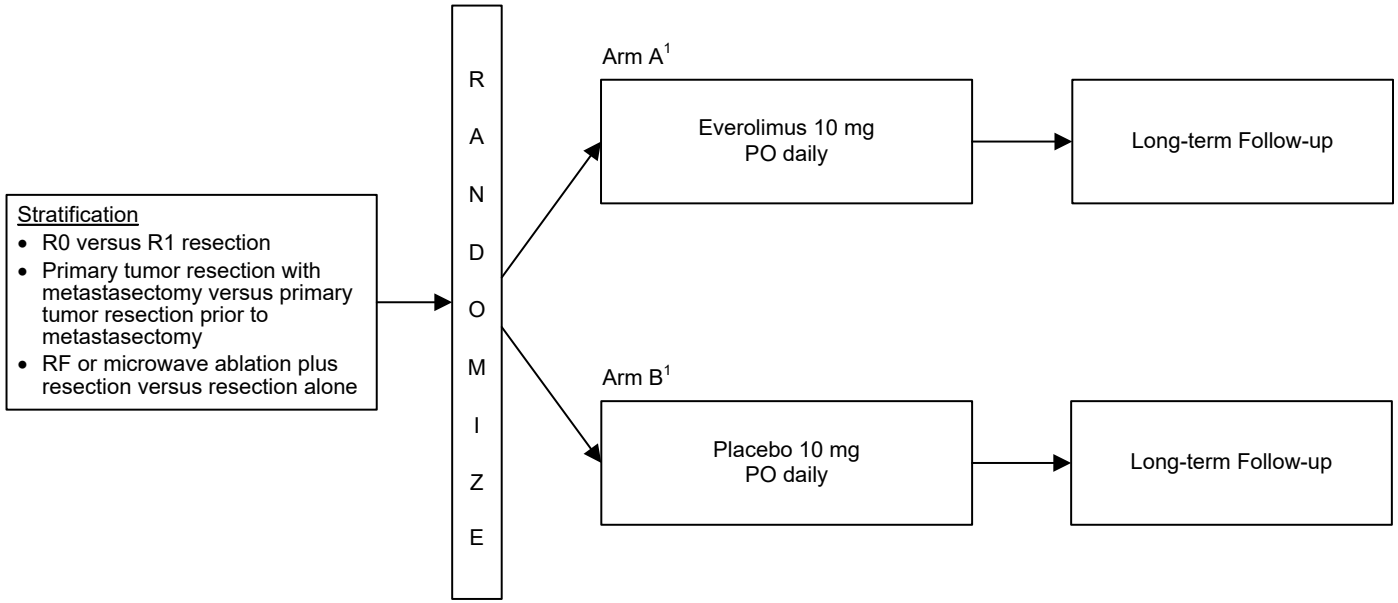
STUDY CHAIR LIAISON (SCL)

Monique White
Montefiore Medical
3400 Bainbridge Avenue
Map Building, Fourth Floor
Bronx, NY 10467
Phone: 718-862-8840
Fax: 718-862-8854
Email: mnwhite@montefiore.org

Rev. 5/14 CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Data collection will be performed exclusively in Medidata Rave:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206	Please refer to the patient enrollment section for instructions on using the OPEN system.	Please refer to the Forms Completion Guidelines for the Forms Submission Schedule.
The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.		
For patient eligibility or treatment-related questions Contact the Study PI of the Coordinating Group.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org		
The CTSU Web site is located at https://www.ctsu.org		

Schema



Accrual Goal: 150 patients
Cycle = 4 week (28 days)

1. Treatment will continue for up to 12 cycles (approximately 1 year).

1. Introduction

Pancreatic neuroendocrine tumors (PNETs) have a spectrum of behavior from indolent to quite aggressive with the liver being the most common site of metastases. Patients with metastatic disease have a median survival of 24 months (1-3). To date, medical treatment options have been limited and include: chemotherapy-based streptozocin and doxorubicin, which has debated efficacy; sunitinib, a tyrosine-kinase inhibitor that appears to have antitumor activity (4-7). More recently, studies of the mammalian target of rapamycin (mTOR), a serine-threonine kinase, demonstrates its role in tumor growth (8). Everolimus, an oral inhibitor of mTOR, appears to confer a statistically significant 6-month prolongation in median disease free survival over placebo in patients with advanced PNETs (4.6 vs. 11.0 months) with a reasonable side effect profile (9).

Despite advances in the medical treatment options for advanced PNETs, only cytoreductive strategies, by way of hepatic resection or ablation, have been shown to significantly improve overall survival or to provide an opportunity for cure (10-12). While the majority of patients recur (94% by 5 years), and while it is difficult to obtain an R0 resection, the morbidity and mortality rates are acceptably low, and surgical resection of liver metastases seems to increase median survival to 125 months (1, 10), more if the patients undergo further hepatectomy following recurrence. For patients undergoing an R0 or R1 resection of liver metastases from a PNET, the median recurrence free survival is 15 months in the largest series and comparable in others (1, 13, 14). Given this knowledge of the survival benefit from surgical metastasectomy and the antiproliferative effect of everolimus, we propose to study a combined medical and surgical approach, to evaluate this combined strategy on both recurrence free survival and overall survival.

Additionally, there is precedent for using targeted agents in the adjuvant setting – specifically imatinib following resection of gastrointestinal stromal tumors (GISTs), which improves recurrence free survival (15, 16). GISTs harbor mutations in the KIT proto-oncogene (85%) and platelet-derived growth factor alpha receptor (3-5%). Imatinib specifically targets these pathways involved in GIST carcinogenesis including KIT, PDGFR A, and other ABL and BCR-ABL tyrosine kinases. Everolimus likewise targets a relevant pathway in NET carcinogenesis as PNETs are known to have mutations in mTOR (17). The concept of adjuvant therapy following surgical metastasectomy as a means of improving time to recurrence has also been validated in the treatment of stage IV colorectal cancer (18).

Trial Design

The trial design would be a prospective, randomized placebo controlled study of adjuvant everolimus (orally at 10 mg per day) versus placebo after surgical resection (with or without ablation) of liver metastases from a PNET to an R0 or R1 resection. Patients will be randomized after surgery. Patients will receive study drug (ARM A) or placebo (ARM B) for approximately 12 months following resection or until recurrence whichever comes first. The current standard of care following resection is no treatment; therefore, placebo is an acceptable control arm in this patient population. The primary endpoint will be recurrence free survival with overall survival as a secondary endpoint. Given that everolimus in patients with advanced PNET improves progression free survival from 4.6 to 11.0 months as seen in the RADIANT-3 study (a > 50% improvement), we would predict that the addition of everolimus to surgical metastasectomy would improve disease free survival from 15 to 27 months (conservatively < 50% improvement).

A prospective randomized double-blinded study is necessary in order to assess impact on disease free survival.

Background For Potential Laboratory Research Studies

Genes are frequently mutated in pancreatic neuroendocrine tumors.

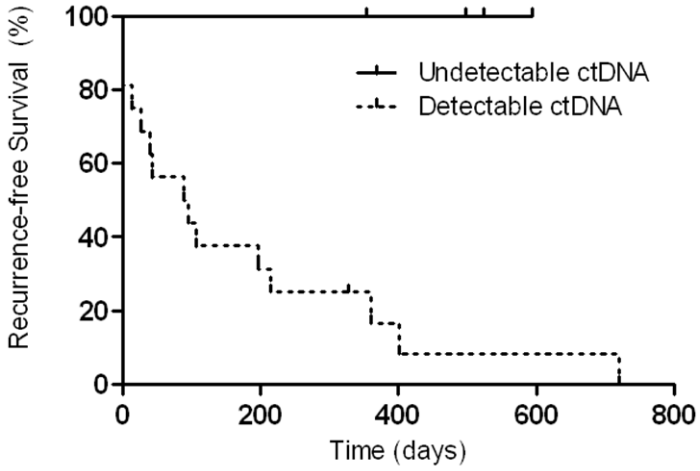
Genes	Frequency Mutated (n=68)
MEN1	44% (30)
DAXX	25% (17)
ATRX	18% (12)
PTEN	7% (2)
TSC2	9% (6)
PIK3CA	1% (1)

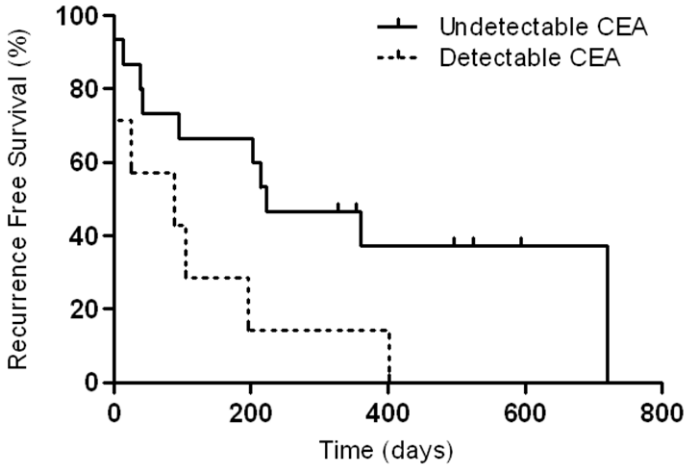
The mutations in the PTEN/PIK3CA/MROT pathway suggests that tumors with activating mutations in this pathway may be preferentially sensitive to treatment with mTOR inhibitors, these patients with tumors that are mutant for PIK3CA, PTEN or TSC may benefit in terms of DFS and OS. Further characterization of the tumors by exploring genes such as MEN1, DAXX, ATRX and mutations in chromatin remodeling may give insight to patient outcome. Mutations in chromatic remodeling have been demonstrated to confer a survival benefit in patients with metastatic neuroendocrine tumors (mOS of 5 years vs. 13 years; HR 0.14; p=0.02).

Small fragments of DNA (165 bp) are released by tumors into the circulation and can be distinguished from DNA fragments released by normal cells using the mutations found in the tumor. Circulating tumor DNA (ctDNA) is only detectable when there is tumor present and quickly disappears from the circulation (half-life ~ 2 hours) after tumor resection. A recent study by our laboratory, applied a digital genomic method to detect and quantify ctDNA in patients with colorectal cancer (21). This approach termed “BEAMing”, which was named after components of this method (Beads, Emulsification, Amplification and Magnetics). This method uses standard laboratory tools and reagents to create a water-in-oil emulsion wherein each aqueous microdroplet houses an individual fragment of DNA bound to a bead. This setting allows billions of compartmentalized polymerase chain reactions (PCR) to be performed in parallel in a single test tube. The products of these reactions coat each bead with thousands of copies of DNA fragments that are identical to the single DNA molecule originally present. In this case, the result is millions of beads coated entirely with either mutant or wild-type DNA. To distinguish mutant from wild-type coated beads, allele-specific fluorescent probes complementary to the known wild-type or mutant sequences are simultaneously added to the beads for hybridization. The beads are then accessed via flow cytometry to detect rare mutant DNA molecules among a much larger number of normal DNA molecules. BEAMing is a digital assay and is able to count the frequency of individual DNA fragments in a sample.

In a cohort of patients with colorectal cancer, tumor response and progression was tracked in patients using ctDNA as a biomarker of tumor burden. For each patient, the mutation profile for his or her tumor was identified from microdissected paraffin embedded tissue. BEAMing assay was used to quantify

ctDNA over time in each patient undergoing multi-modality treatment for colorectal cancer over the course of 1-2 years. The results from this study demonstrated that ctDNA could be used a biomarker of tumor burden and that dynamic changes in ctDNA levels correlated with tumor response and progression (Figure, below). Of note, ctDNA was detected in 100% of patients evaluated. In addition, ctDNA was significantly more sensitive than the standard protein biomarker used in colorectal cancer monitoring (CEA – Carcinoembryonic Antigen). One of the most promising aspects of this study was showing that ctDNA was sufficiently sensitive to detect minimal residual disease after surgical resection with curative-intent (Figures, below), thereby detecting micrometastatic disease and recurrence before it was evident with traditional protein biomarkers or imaging.





2. Objectives

Primary objective:

2.1.1 To evaluate if the addition of adjuvant everolimus to the R0 or R1 surgical resection of pancreatic neuroendocrine tumor metastases to the liver will result in an improvement in disease free survival.

Secondary objectives:

2.2.1 To evaluate if the addition of adjuvant everolimus to the R0 or R1 surgical resection of pancreatic neuroendocrine tumor metastases to the liver will result in an improvement in overall survival.

2.2.2 To evaluate the toxicity associated with adjuvant everolimus following resection in patients with metastatic pancreatic neuroendocrine tumors to the liver.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to randomization by the treating physician.

Eligibility: Criteria

_____ 3.1.1 Patients must have histologically or pathologically confirmed metastatic low or intermediate grade pancreatic neuroendocrine tumor(s) to the liver as per the Klimstra guidelines (20).

_____ 3.1.2 Patients must have recovered from an R0 or R1 resection of all disease (including resection of a primary PNET if present). Patients may have had resection plus microwave or radiofrequency ablation, provided that no ablated lesion was ≥ 5 cm prior to ablation.

_____ 3.1.3 Patients must be within 4 to 8 weeks from the completion of surgery at time of randomization.

_____ 3.1.4 Patients must have paraffin-embedded fixed metastatic tumor tissue available for submission for central review per Sections 10 and 11. Core biopsy or surgical specimens required.

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_____ 3.1.5 Patients must have post-operative CT or MRI to confirm no evidence of disease within 4 weeks prior to randomization. Patients must be able to tolerate CT or MRI imaging including contrast agents as required for the protocol.

_____ 3.1.6 Patients must NOT have either clinically apparent central nervous system metastases or carcinomatous meningitis ≤ 6 months prior to randomization.

_____ 3.1.7 Women must NOT be pregnant or breast-feeding due to possible risk involved in taking everolimus.

All females of childbearing potential must have a blood test within 2 weeks prior to randomization to rule out pregnancy. A female of childbearing potential is any female, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at

least 24 consecutive months (i.e. has had menses at any time in the preceding 24 consecutive months).

Female? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.1.8 Women of child-bearing potential and sexually active males must be strongly advised to use an accepted and highly effective method of contraception or abstain from sexual intercourse for the duration of their treatment through 8 weeks after their last dose of protocol therapy. Women of child-bearing potential, sexually active males, and the female partners of male participants should be advised of the risk or becoming pregnant or fathering a child while receiving protocol treatment. Should a woman become pregnant while participating in this study, she should inform her treating physician immediately. If a man impregnates a woman while participating in this study, he should inform his treating physician immediately. See Section 8.1.14 for information on methods of contraception.

_____ 3.1.9 Prior treatment with sunitinib and/or cytotoxic chemotherapy are allowed provided last dose was > 30 days prior to randomization.

_____ 3.1.10 Prior chemoembolization is allowed provided last dose was > 30 days prior to randomization.

_____ 3.1.11 Patients must NOT have received prior everolimus.

_____ 3.1.12 Patients may not be receiving any other investigational agents while on study treatment. Prior treatment with other investigational agent is allowed provided last dose was > 30 day prior to randomization.

_____ 3.1.13 Patients must have normal organ and marrow function as defined below within ≤ 4 weeks prior to randomization:

_____ 3.1.13.1 Total bilirubin ≤ 1.5 X institutional upper limit of normal (ULN)

ULN: _____ Bilirubin:_____ Date:_____

_____ 3.1.13.2 AST(SGOT)/ALT(SGPT) ≤ 5 X institutional ULN

ULN: _____ AST_____ Date:_____

ULN: _____ ALT_____ Date:_____

_____ 3.1.13.3 Serum creatinine ≤ 1.5 X institutional ULN or creatinine clearance ≥ 60 mL/min for patients with creatinine levels above 1.5 X institutional normal.

ULN: _____ Creatinine: _____ Date:_____

Creatinine clearance: _____ Date:_____

_____ 3.1.13.4 Fasting serum total cholesterol ≤ 300 mg/dL OR ≤ 7.75 mmol/L AND fasting triglycerides ≤ 2.5x ULN.

NOTE: If one or both of these thresholds are exceeded, the patient can only be randomized after initiation of appropriate lipid lowering medication

Fasting serum cholesterol: _____ Date:_____
Fasting triglycerides: _____ Date:_____
Lipid lowering medication: _____ (Yes or No)

_____ 3.1.13.5 Absolute neutrophil count ≥ 1,500/mm^3

Neutrophil count: _____ Date:_____

_____ 3.1.13.6 Leukocytes ≥ 3,000/mm^3

Leukocytes: _____ Date:_____

_____ 3.1.13.7 Platelets ≥ 100,000/mm^3

Platelets: _____ Date:_____

_____ 3.1.13.8 Hemoglobin ≥ 9 g/dL

Hemoglobin: _____ Date: _____

_____ 3.1.14 Patients must NOT have ongoing cardiac dysrhythmia of NCI CTCAE v4.0 Grade ≥ 2, uncontrolled atrial fibrillation of any grade, or QTc interval > 470 msec.

_____ 3.1.15 Patients with a history of the following within ≤ 12 months of randomization are not eligible.

- Arterial thromboembolic events: Yes____ Date:_____ No:_____
- Unstable angina: Yes_____ Date:_____ No:_____
- Myocardial Infarction: Yes_____ Date:_____ No:_____

_____ 3.1.16 Patients must NOT have experienced thrombotic events (deep vein thrombosis, pulmonary embolism) ≤ 3 months prior to randomization.

_____ 3.1.17 Patients must NOT have liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis at randomization. Patients at increased risk for hepatitis B or hepatitis C per Appendix VIII must be screened for hepatitis prior to randomization.

_____ 3.1.18 Patients must NOT have history of severely impaired pulmonary function for their age due to the risk of noninfectious pneumonitis. Patients with known history of abnormal pulmonary function must have documentation of DLCO of > 50% predicted and SaO_2 of > 87% at rest on room air ≤ 4 weeks prior to randomization.

_____ 3.1.19 Patients with unexplained pulmonary infiltrates must have pulmonary function tests within the institutional limits of normal ≤ 4 weeks prior to randomization.

_____ 3.1.20 Patients with known history of HIV seropositivity are ineligible due to lack of safety data on combining antiretroviral therapy, the immunosuppressive effects of everolimus and the risk of opportunistic infection.

_____ 3.1.21 Patients with poorly controlled diabetes mellitus as defined by HbA1c > 8% despite adequate therapy are ineligible. Patients with a known history of impaired fasting glucose or diabetes mellitus must have blood glucose and antidiabetic treatment monitored closely throughout the trial and adjusted as necessary.

_____ 3.1.22 Patients must NOT have any severe and/or uncontrolled medical conditions such as:

a. unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months prior to randomization, serious uncontrolled cardiac arrhythmia, or any other clinically significant cardiac disease

b. Symptomatic congestive heart failure of New York Heart Association Class III or IV

c. active (acute or chronic) or uncontrolled severe infection, liver disease such as cirrhosis, decompensated liver disease, and chronic hepatitis (i.e. quantifiable HBV-DNA and/or positive HbsAg, quantifiable HCV-RNA)

d. active, bleeding diathesis

_____ 3.1.23 Patients must NOT have previous or concurrent malignancy. Exceptions are made for patients who meet any of the following conditions:

- Non-melanoma skin cancer, in situ cervical cancer, breast cancer in situ, or superficial bladder cancer (noninvasive papillary carcinoma or carcinoma in situ).

OR

- Prior malignancy completely excised or removed and patient has been continuously disease free for > 5 years.

Date of last evidence of disease: _____

_____ 3.1.24 Patients may not be receiving any other investigational agents while on study treatment. Prior treatment with other investigational agent is allowed provided last dose was ≥ 30 days prior to randomization.

_____ 3.1.25 Patients must NOT have received live attenuated vaccines ≤ 1 week prior to randomization. Patients should also be advised not to receive live attenuated vaccines during the study and to avoid close contact with others who have received live attenuated vaccines. Examples of live attenuated vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines.

_____ 3.1.26 Patients must NOT be on chronic treatment with corticosteroids or other immunosuppressive agents. Topical or inhaled corticosteroids are allowed.

_____ 3.1.27 Patients should be advised to avoid drugs or foods that are known potent CYP3A4 inhibitors or inducers, included but not limited to those outlined in Appendix V.

_____ 3.1.28 Patients must NOT have history of allergic reactions attributed to compounds of similar chemical or biologic composition to everolimus.

_____ 3.1.29 Patients must NOT have known intolerance or hypersensitivity to everolimus or other rapamycin analogs (e.g. sirolimus, temsirolimus).

_____ 3.1.30 Patients must NOT have absorption issues that would limit the ability to absorb everolimus.

_____ 3.1.31 Patients must NOT have a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study.

_____ 3.1.32 Patients must be at least ≥ 18 years of age.

_____ 3.1.33 Patients must have ECOG performance status ≤ 1. (Refer to Appendix IV)

_____ 3.1.34 Patients must have life expectancy ≥ 12 weeks.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

4. Randomization Procedures

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This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at *https://www.ctsu.org*; then click on the Register tab) or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at *https://www.ctsu.org*.

Requirements for E2212 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Submitting Regulatory Documents

Before an ECOG-ACRIN Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX: (215) 569-0206

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.
2. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter.

NOTE: The above submissions must include the following details:

- Indicate all sites approved for the protocol under an assurance number.
- OHRP assurance number of reviewing IRB
- Full protocol title and number
- Version Date
- Type of review (full board vs. expedited)
- Date of review.
- Signature of IRB official

The CTSU encourages you to link to the following RSS2.0 webpage so that more information on RSS2.0 as well as the submission forms can be accessed. Log in to http://www.ctsu.org and click on the Regulatory tab to access the RSS web page. If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail CTSUContact@westat.com.

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Patients must not start protocol treatment prior to randomization.

Treatment must start within five working days after randomization.

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Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

All site staff (Lead Group and CTSU Sites) will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

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Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Randomization

Please note that no blinded starter supplies will be available for this study. At the time of patient randomization each patient will be assigned a specific blinded drug ID number (e.g. DR117). This blinded drug ID number should be included on the drug request form that is submitted to the ECOG-ACRIN Drug Team. (See Section 8 for complete details.)

Please note that when a patient has been successfully randomized, the confirmation of randomization will indicate that the patient is on arm X. The patient will actually be randomized to arm A or B, but as this is a double-blind trial, that information cannot be displayed.

At time of randomization, the following information will be requested:

4.1.1 Protocol Number

4.1.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.

Stratification Factors

Stratification will only be used to ensure balance between groups, not for subset analysis. There are three stratification factors as follows:

4.3.1 R0 versus R1 resection

4.3.2 Primary tumor resection

4.3.2.1 Primary tumor resection with metastasectomy

4.3.2.2 Primary tumor resection prior to metastasectomy

4.3.3 Resection ± ablation

4.3.3.1 RF or microwave ablation plus resection

4.3.3.2 Resection alone

Additional Requirements

4.4.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.4.2 Pathological samples are **required** to be submitted for central diagnostic review as indicated in Section 10.

4.4.3 Biological samples to be submitted for research as outlined in Section 10.

4.4.4 Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS. To access iMedidata/Rave the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam). In addition, site users that are a member of ECOG-ACRIN must have the mapped ECOG-ACRIN roles or explicit Rave roles (Rave CRA, Read-Only, Site Investigator) in RSS at the enrolling site. Site users that are not members of ECOG-ACRIN must have the Rave roles on the CTSU roster at the enrolling sites. The Site Administrator or Data Administrator at the enrolling site may assign the appropriate roles from the Site Roles tab on the CTSU website.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at http://www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

4.5 Investigator's Drug Brochure and Safety Alerts

The Investigator Drug Brochure (IDB) for everolimus is available for download from the ECOG-ACRIN webpage. The IDB provides relevant and current scientific information about the investigational product. The IDB should be submitted to your IRB/EC according to GCP regulations. The IDB and any correspondence to the Institutional Review Board (IRB)/Ethics Committee (EC) should be kept in the E2212 regulatory files.

Should any SAE report on this study qualify as a safety alert report requiring expedited reporting, the SAE report will be sent by the respective pharmaceutical company to regulatory authorities globally (including the FDA) and ECOG-ACRIN. If applicable, ECOG-ACRIN will disseminate these safety alert reports to all ECOG-ACRIN investigators in the bimonthly group mailings. These reports should be forwarded to your IRB/EC within 90 days of receipt for review. Reporting instructions are provided with each safety alert. These safety alerts and any correspondence to your IRB/EC should be maintained in your E2212 study files.

IND Status

When used in this protocol. Everolimus/placebo are each classified as an "unapproved use of an approved agent" and by definition considered investigational agents. However, while it is not an indication currently approved by the FDA, the use of everolimus/placebo in this protocol is exempt from the requirements of an IND and described under Title 21 CFR 312.2(b).

Emergency Unblinding

The information provided below is for the use by a physician, nurse, CRA or pharmacist treating the patient. These contact numbers should not be used by patients. Patients should be instructed to call their doctor's office in the event of an emergency or adverse event that may result in the need to unblind the patient.

In the event of an emergency or severe adverse reaction necessitating identification of the medication for the welfare of the patient, please contact the Study Chair, Dr. Steven Libutti M.D., at 718-920-4231 or Email slibutti@montefiore.org, first to ensure the reason for unblinding is valid. Then call a member of the ECOG-ACRIN Operations Office – Boston drug team at (617) 632-3610 Monday through Friday between 9:00 AM and 5:00 PM Eastern Time. For unblinding outside of these hours, contact AnswerConnect at 1-866-296-8940. This service will request the reason for unblinding and then page the on-call ECOG-ACRIN staff who will return your call and provide the unblinded treatment assignment if applicable. Remember, AnswerConnect should only be contacted outside of normal business hours and only in the event of an emergency. The ECOG-ACRIN Operations Office – Boston or AnswerConnect will require the protocol number (i.e., "E2212"), the patient ID number (e.g., "44444"), and the patient initials (e.g., "FL") to unblind the patient. Note that if a patient is unblinded, he/she must discontinue protocol treatment.

Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the E2212 Forms Completion Guidelines.

5. Treatment Plan

Administration Schedule

One cycle = 28 days.

NOTE: Everolimus/placbo is packaged in blister cards of ten 5 mg tablets; patients should receive 6 blister cards (30 doses) for each 28 day cycle. The start of each treatment cycle may be scheduled up to 2 days later than the expected Day 1 of that cycle.

Patients should take everolimus/placebo, 10 mg, orally once daily at the same time every day, either consistently with food or consistently without food.

A missed dose may still be taken up to 6 hours after the normally scheduled time. If more than 6 hours have elapsed, patient should be instructed to skip the dose for that day. The next day, they should take everolimus/placebo at the usual time. Patients should not take 2 doses to make up for the one that they missed.

If vomiting occurs, no attempt should be made to replace the vomited dose.

Everolimus/placebo tablets should not be crushed or chewed. Tablets should be swallowed whole with a glass of water. For patients unable to swallow tablets, everolimus/placebo tablets should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring, immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse should be completely swallowed to ensure that the entire dose is administered.

5.1.1 Treatment/ARM A

Everolimus 10 mg PO daily

Repeat cycles every 28 days for a maximum duration of 12 cycles.

5.1.2 Treatment/ARM B

Placebo PO daily

Repeat cycles every 28 days for a maximum duration of 12 cycles.

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Adverse Event Reporting Requirements

5.2.1 **Purpose**

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting**: Adverse events are reported in a routine manner at scheduled times during a trial using Medidata Rave.
- **Expedited reporting**: In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

5.2.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to treatment.
Unlikely	The AE is *doubtfully related* to treatment.
Possible	The AE *may be related* to treatment.
Probable	The AE is *likely related* to treatment.
Definite	The AE is *clearly related* to treatment.

- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  - A congenital anomaly/birth defect.
  - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

5.2.3 Reporting Procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A

CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.4 Determination of Reporting Requirements

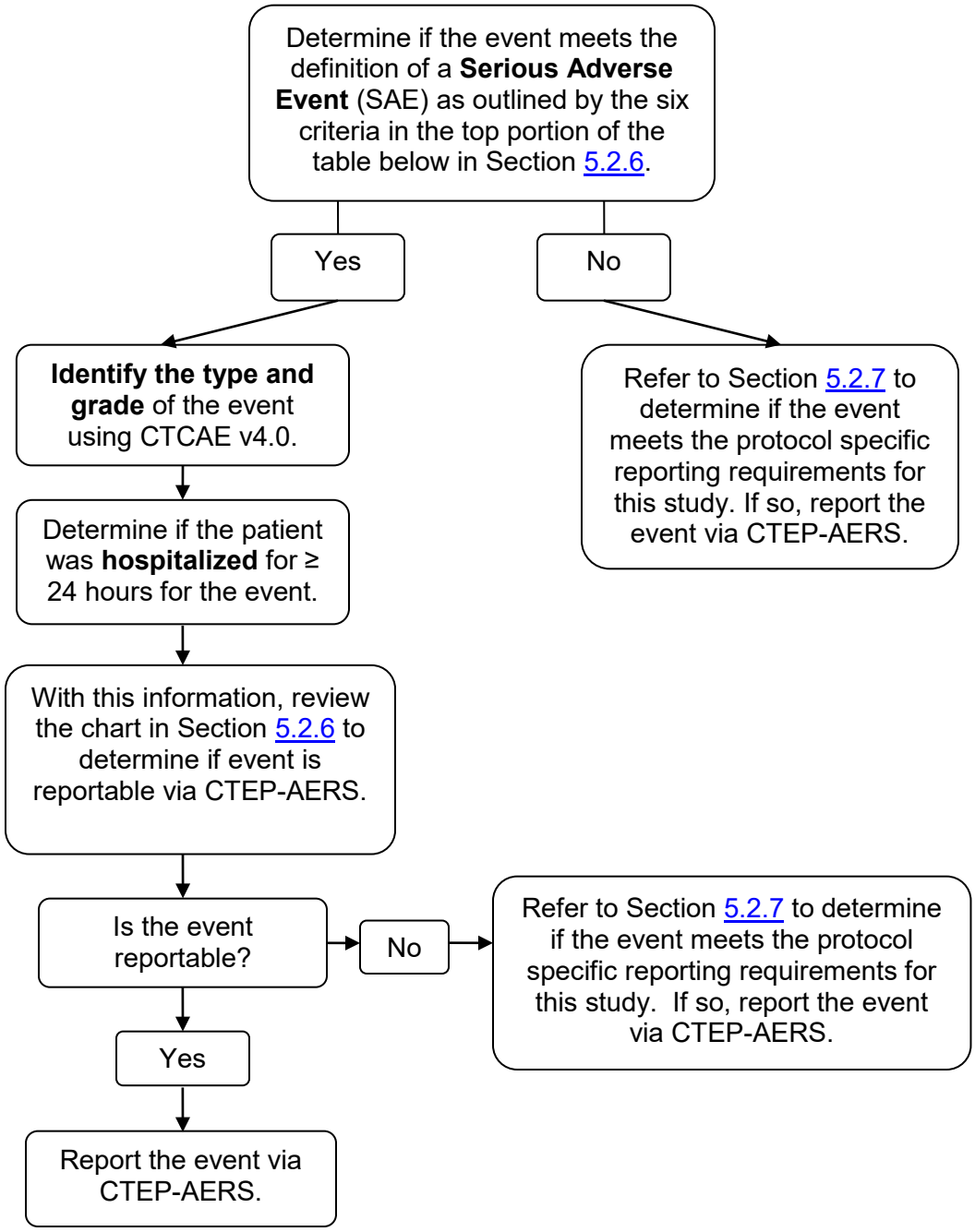
Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event
- when the adverse event occurred (within 30 days of the last administration of everolimus/placebo vs. ≥ 30 days after the last administration of everolimus/placebo)
- the relationship to the study treatment (attribution)

Using these factors, the instructions and tables in the following sections have been customized for protocol E2212 and outline the specific expedited adverse event reporting requirements for study E2212.

5.2.5 Steps to determine if an adverse event is to be reported in an expedited manner

5.2.5.1 Guidelines for adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the everolimus/placebo.



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5.2.5.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the everolimus/placebo.

If the adverse event meets the definition of a **Serious Adverse Event (SAE)** as outlined by the six criteria in the top portion of the table below in Section 5.2.5.2, AND has an attribution of possible, probably or definite, the following events require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and 5 adverse events

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported via CTEP-AERS even if the patient is off study.

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

5.2.6 **Expedited Reporting Requirements for Arm X (Arm A or B) on Protocol E2212**

Investigational Agents: Everolimus/Placebo

Commercial Agents: None

NOTE: Although the agents used on this protocol are IND exempt, the adverse event investigational reporting requirements will be used on this protocol.

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Late Phase 2 and Phase 3 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND *within 30 Days of the Last Administration of the Investigational Agent/Intervention.*[1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" – The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

5.2.7 Additional instructions, requirements and exceptions for protocol E2212

Additional Instructions:

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

E2212 specific expedited reporting requirements:

- **Pregnancy**

  Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state)

occurring while the subject is on Everolimus/Placebo, or within 28 days of the subject's last dose of Everolimus/Placebo, are considered immediately reportable events. **The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge.**

Please refer to Appendix VI for detailed instructions on how to the occurrence of a pregnancy as well as the outcome of all pregnancies.

5.2.8 Other recipients of adverse event reports and supplemental data

ECOG-ACRIN will forward CTEP-AERS reports to the appropriate regulatory agencies and Novartis within 24 hours of receipt.

A drug supporter representative may call a site for additional or supplemental information regarding a serious adverse event. Any additional written AE information requested by the drug supporter MUST be submitted to BOTH ECOG-ACRIN and the drug supporter.

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.9 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

- Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy.

3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

Dose Modifications

5.3.1 General

If dose reduction is required, reduction is permanent. Missed doses may be taken up to 6 hours after normally scheduled time. If more than 6 hours have elapsed, patient should be instructed to skip the dose for that day. The next day, they should take everolimus/placebo at the usual time. Patients should not take 2 doses to make up for the one that they missed.

If multiple toxicities are seen, the dose administered in a subsequent cycle should be based on the most severe toxicity experienced in the current cycle.

AEs determined to be unrelated to study treatment will not require dose reduction.

If everolimus/placebo is held for > 4 weeks (28 days), patient must discontinue protocol treatment.

All toxicities should be graded according to the Common Terminology Criteria for Adverse Events (version 4.0).

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

5.3.2 Everolimus/Placebo Dose Modifications

- For individual subjects, dose modifications will be based on hematologic or non-hematologic toxicity, laboratory test results,

and clinical assessment on the day of treatment and during the previous cycle.

- If dose delays are required, weekly evaluation with laboratory tests and clinical assessments, if applicable, should be performed until recovery to the specified grade or until the subject is discontinued from the study.
- If toxicities have not resolved within ≤ 4 weeks (28 days), patient must discontinue protocol treatment.
- The study chair or study chair liaison should be contacted for dose delays and modifications for all other toxicities not listed in this section.
- One dose reduction is permitted before everolimus/placebo will be discontinued. Patients who require further dose reductions beyond the -1 dose level must be discontinued from study treatment.

Everolimus/Placebo Dose Level Table	
Dose Level	Dose in mg
0	10 mg daily
-1	5 mg daily

5.3.2.1 Management of Hematologic Toxicity

Toxicity	**Action**
Grade 2 Platelet count decreased	No action
Grade 3 Platelet count decreased	Interrupt everolimus/placebo until resolution to grade ≤ 1 If resolution occurs ≤ 7 days, reintroduce everolimus/placebo at the dose level prior to interruption. If resolution occurs > 7 days, or event occurs within 28 days, reintroduce everolimus/placebo at one dose level lower, if available.
Grade 4 Platelet count decreased	Interrupt everolimus/placebo until recovery to grade ≤ 1. Then reintroduce everolimus/placebo at one dose level lower, if available.
Grade 3 Neutrophil count decreased	Interrupt everolimus/placebo until resolution to grade ≤ 1 or baseline value If AE resolution occurs ≤ 7 days, reintroduce everolimus/placebo at the same dose level. If AE resolution occurs > 7 days, or event occurs within 28 days, reintroduce everolimus/placebo at one dose level lower, if available.
Grade 4 Neutrophil count decreased or grade 4 Anemia	Interrupt everolimus/placebo until recovery to grade ≤ 1 or baseline value. Reintroduce everolimus/placebo at one dose level lower, if available.
Febrile neutropenia	Interrupt everolimus/placebo until resolution to grade ≤ 1 (or baseline value) and no fever. Reintroduce everolimus/placebo at one dose level lower, if available.
Recurrence of grade 3 hematologic toxicity after dose reduction	Reduce dose to the next lower dose level, if available.

Recurrence of grade 4 hematologic toxicity (including febrile neutropenia) after dose reduction	**Discontinue protocol treatment.**
Any hematologic toxicity requiring everolimus/placebo interruption for > 28 days	**Discontinue protocol treatment.**

5.3.2.2 Non-Hematologic Toxicity

Toxicity	**Action**
AST or ALT elevation Grade 1 (> ULN - 3.0 x ULN) Grade 2 (> 3.0 - 5.0 x ULN)	Maintain current dose level
AST or ALT elevation Grade 3 (> 5.0 - 20.0 ULN)	Interrupt everolimus/placebo administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs ≤ 7 days, everolimus/placebo should be re-started at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 28 days, hold everolimus/placebo until recovery to ≤ grade 1 or baseline grade / value and reintroduce everolimus/placebo at one dose level lower, if available.
AST or ALT elevation Grade 4 (> 20 x ULN)	Interrupt everolimus/placebo administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs ≤ 7 days, everolimus/placebo should be re-started at one dose level lower. If resolution takes > 7 days, discontinue everolimus/placebo.
Intolerable grade 3 AE, except hyperglycemia or hypertriglyceridemia or hypercholesterolemia	Interrupt everolimus/placebo administration until resolution to ≤ grade 1 or baseline grade / value. If resolution occurs within ≤ 7 days, everolimus/placebo should be re-started at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 28 days, hold everolimus/placebo until recovery to ≤ grade 1 or baseline grade / value and reintroduce everolimus/placebo at one dose level lower, if available. Patients will be withdrawn from the study if they fail to recover to ≤ grade 1 or baseline grade / value within 28 days.
Any other grade 4 non-hematologic	Hold everolimus/placebo until recovery to grade ≤ 1 or baseline value Reintroduce everolimus/placebo at one dose level lower, if available.
Grade 3 or 4 clinical liver failure (asterixis or encephalopathy/coma)	Discontinue everolimus/placebo
Recurrence of intolerable grade 2 mucositis or grade 3 event after dose reduction	Reduce dose to the next lower dose level, if available.
Recurrence of grade 4 non-hematologic toxicity after dose reduction	**Discontinue protocol treatment.**
Any non-hematologic toxicity requiring Everolimus/Placebo interruption for > 28 days	**Discontinue protocol treatment.**

5.3.2.2.1 Mucositis[1]

Category	Grade	Everolimus/placebo dose modification
Mucositis oral	Grades 1	No dose modification.
	Grades 2-4	Hold until ≤ grade 1 then reduce by one dose level.

1 Please refer to Section 5.4.2 for mucositis and stomatitis supportive care information.

5.3.2.2.2 Stomatitis[1]

Adverse Drug Reaction	Severity	Everolimus/Placebo Dose Adjustment and Management Recommendations
Stomatitis	Grade 1	No dose adjustment required.
	Grade 2	Hold until grade ≤1. Re-initiate everolimus/placebo at same dose. If stomatitis recurs at grade 2, hold until ≤ grade 1 then reduce by one dose level.
	Grade 3	Hold until ≤ grade 1 then reduce by one dose level.
	Grade 4	Discontinue protocol therapy and treat with appropriate medical therapy.

1. Please refer to Section 5.4.2 for mucositis and stomatitis supportive care information.

5.3.2.2.3 Diarrhea

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

5.3.2.2.4 Metabolic Events: Hyperlipidemia and Hyperglycemia

Hyperglycemia has been reported in clinical trials. Monitoring of fasting serum glucose is recommended prior to the start of everolimus/placebo and periodically thereafter. Optimal glycemic control should be achieved before starting a patient on everolimus/placebo.

Category	Grade	Everolimus/Placebo Dose Adjustment and Management Recommendations
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
	Grade 3	Hold until ≤ grade 1 then reduce by one dose level. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue protocol therapy and treat with appropriate medical therapy.

5.3.2.2.5 Pulmonary Toxicity

Category	Grade	Everolimus/placebo dose modification
Vital Capacity Abnormal	Grades 1	Obtain CT scan with lung windows. Continue previous dose of treatment.
	Grade 2	Obtain CT scan with lung windows. Obtain pulmonary function testing including spirometry, DLCO, and room air O2 saturation at rest. Hold protocol treatment until toxicity improves to ≤ grade 1, then resume with one dose level reduction of treatment. Steroids may be used at the discretion of the treating physician for relief of symptoms associated with pulmonary toxicity.
	Grade 3	Obtain CT scan with lung windows and pulmonary function testing including spirometry, DLCO, room air O2 saturation at rest, and bronchoscopy. Hold protocol treatment until recovery to ≤ grade 1, then resume treatment with one dose level reduction. Steroids may be used at the discretion of the treating physician for relief of symptoms associated with pulmonary toxicity.
	Grade 4	Obtain CT scan with lung windows and pulmonary function testing including spirometry, DLCO, room air O2 saturation at rest, and bronchoscopy. Discontinue protocol treatment. Steroids may be used at the discretion of the treating physician for relief of symptoms associated with pulmonary toxicity.

5.3.2.2.6 Non-Infectious Pneumonitis

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

A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Patients should

be advised to report promptly any new or worsening respiratory symptoms.

Consultation with a pulmonologist is recommended for any case of pneumonitis that develops during the study.

Worst grade pneumonitis	Suggested investigations	Management of pneumonitis	Everolimus/placebo dose adjustment
Grade 1	CT scans with lung windows.	No specific therapy is required	No dose adjustment required. Initiate appropriate monitoring.
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Consider a bronchoscopy with biopsy and/or BAL. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence.	Symptomatic only. Consider corticosteroids and/or other supportive therapy if symptoms are troublesome.	Rule out infection and consider interruption of Everolimus/placebo until symptoms improve to Grade ≤ 1. Re-initiate Everolimus/placebo at one dose level lower. Discontinue Everolimus/placebo if failure to recover within ≤ 28 days.
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and interrupt Everolimus/placebo until symptoms improve to Grade ≤ 1. Consider re-initiating Everolimus/placebo at one dose level lower. Discontinue protocol therapy if failure to recover within ≤ 28 days.
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and discontinue protocol ttreatment.

5.3.2.2.7 Infections

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

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

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

Supportive Care

5.4.1 All supportive measures consistent with optimal patient care will be given throughout the study.

5.4.2 Mucositis, Stomatitis, and Mouth Ulcers

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

Stomatitis/oral mucositis/mouth ulcers due to Everolimus/placebo should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with Everolimus/placebo as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify

the adverse event as such. The suggested paradigm for treatment of stomatitis/oral mucositis/mouth ulcers is as follows:

1. For mild toxicity (grade 1), no dose adjustment required. Manage with non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
2. For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
3. Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. These agents should be avoided.
4. Antifungal agents should be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of Everolimus/placebo metabolism, therefore leading to higher Everolimus/placebo exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed.

Duration of Therapy

Patients will receive protocol therapy unless:

5.5.1 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the **E2212** Forms Completion Guidelines.

5.5.2 Patient withdraws consent.

5.5.3 Patient experiences unacceptable toxicity.

5.5.4 Non-protocol cancer therapies are administered.

5.5.5 Disease recurrence per protocol criteria, development of new primary cancer, or death.

5.5.6 Patient completes 12 cycles of therapy.

5.5.7 Patient is unblinded.

Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until disease recurrence, even if non-protocol therapy is initiated, and for survival for 5 years from the date of randomization. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

Local, Regional Disease

The development of a local or regional pancreatic neuroendocrine cancer.

Distant Disease

The development of a distant recurrence of pancreatic neuroendocrine cancer.

Disease-Free Survival

Date of randomization to the date of documented recurrence (a return of tumor imaged by CT or MRI), new invasive primary cancer, or death without recurrence

Survival

Date of randomization to date of death.

Second primary cancer

The diagnosis of a second primary cancer must be confirmed histologically whenever possible.

7. Study Parameters

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1. Prestudy CT scan or MRI must be done after surgery and ≤ 4 weeks before randomization.
2. Prestudy CBC (with differential and platelet count) must be done ≤ 4 weeks before randomization.
3. All required prestudy chemistries and hepatitis antibody lab panels must be performed ≤ 4 weeks randomization unless otherwise specified in Section 3.

	Prior to Randomization	Day 1 of each cycle	Every 3 cycles (every 12 weeks)	End of Treatment[13]	At recurrence[8]	Follow-up[7]
History and Progress Notes	X	X		X		X
Physical Exam	X	X		X		X
Vital Signs	X	X		X		
Weight/BSA	X	X		X		
ECOG Performance Status	X	X		X		
Adverse Event Assessment[11]		X		X		X[11]
CBC with Differential[1]	X	X		X		
Serum Chemistry and Electrolytes[2]	X	X		X		
Lipid Panel[2]	X	X				
Blood/Urine Pregnancy Test[3,4]	X	X[4]		X		
Hepatitis Antibody Lab Panels[12]	X					
Patient table calendar		X		X		
Multiphasic CT Scan (Chest, Abdomen and Pelvis) or MRI of Abdomen and Pelvis with CT Scan of Chest[9]	X		X	X	X	X
CgA, NSE level and hemoglobin A1c[10]	X		X	X	X	X
Tumor Measurement					X	
Pathology and surgery reports	X				X	
Specimen Submissions: Specimens to be submitted within 4 weeks following randomization. See Section 10.						
MANDATORY: Pre-trial FFPE tumor[5]	X					
Frozen Surgical Tumor Tissue[6]	X					
Peripheral Blood, ACD vacutainer[6]		Prior to start of treatment		X		
Plasma from EDTA[6]				X		

1. CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct required for protocol therapy must be done ≤ 24 hours prior to Cycle 1 Day 1, ≤ 72 hours prior to Day 1 of all subsequent cycles.

2. Serum electrolytes: Glucose, Na+, K+, bicarbonate, BUN, Cl, creatinine. Other serum chemistries: Albumin, total protein, alkaline phosphatase, SGOT(AST), SGPT(ALT), total bilirubin; Ca++. Lipid Panel: Serum fasting cholesterol and serum triglycerides. Serum electrolytes, chemistries, and lipid panel must be done ≤ 72 hours prior to each treatment cycle.
3. Women of childbearing potential only. Serum pregnancy test must be performed ≤ 14 days prior to randomization and at the end of study treatment. Urine pregnancy testing should be performed prior to each treatment cycle at the physician's discretion.
4. Urine pregnancy testing should be performed prior to each treatment cycle at the physician's discretion.
5. Diagnostic metastatic tumor tissue (core biopsy or surgical specimen, liver mets, and diagnostic slides) must be submitted for central diagnostic review and classification and for optional laboratory research studies within 4 weeks following randomization as outlined in Section 10. Failure to submit the required materials may render the case unevaluable.
6. Research samples are to be submitted from patients who consent to allow the samples to be submitted for research as outlined in Section 10. It is requested that the "prior to start of treatment" blood draws occur 6-8 weeks after surgery, prior to start of protocol therapy. Please indicate date of surgery in STS.
7. Every 3 months if patient is < 2 years from study entry; every 6 months if patient is 2-5 years from study entry. Once there is confirmation of recurrence, follow-up scans, CgA, NSE level, and hemoglobin A1c no longer have to be performed; patient must continue to be followed for survival.
8. It is strongly encouraged that disease recurrence documented by scans also be confirmed by biopsy. If there is a recurrence, it is also strongly encouraged that patients be fully restaged, including a CT scan of the thorax and abdomen, imaging (preferably MRI, but CT is acceptable) of the brain.
9. Rev. 5/14, 5/14 Baseline CT or MRI scans must be done after surgery and ≤ 4 weeks prior to randomization. After randomization, the CT Scan or MRI may be scheduled with a ± 2 week leeway. The scheduling of the last on-treatment scan may be moved up or delayed up to 6 weeks to also meet the end of treatment time frame.
10. Chromogranin A (CgA), neuron-specific enolase (NSE) level and hemoglobin A1c should be performed at the same time scans are performed. If other tumor markers (i.e., glucagon, insulin, VIP, pancreatic polypeptide, gastrin) are obtained at baseline and found to be elevated, it is suggested to continue to follow those markers at the time points at which CgA, NSE and hemoglobin A1c are also being followed.
11. Adverse events should be assessed 30 days after the last dose of study drug.
12. Patients with increased risk or history of hepatitis only. See Appendix VIII.
13. End of treatment assessments should be performed ≤ 14 days after going off treatment.

8. Drug Formulation and Procurement

Everolimus/Placebo

8.1.1 Drug Orders

Everolimus and matching placebo are being provided free of charge by Novartis and will be distributed by UVI. The 5 mg tablets of everolimus/placebo will be packaged in 10 tablets per blister pack.

IND Status

When used in this protocol, everolimus/placebo are each classified as an "unapproved use of an approved agent" and by definition considered investigational agents. However, while it is not an indication currently approved by the FDA, the use of everolimus/placebo in this protocol is exempt from the requirements of an IND and described under Title 21 CFR 312.2(b).

Initial Orders: Following submission of the required regulatory documents and patient randomization, a supply of everolimus/placebo may be ordered. Institutions must electronically submit the completed E2212 Drug Request Form to the ECOG-ACRIN Drug Team at 900.drugorder@jimmy.harvard.edu. The drug order form can be found in Appendix VI and is also available for download on the ECOG Web Site. If email is not available, the completed form may be faxed to ATTN: ECOG-ACRIN Drug Team at 617-632-2063. No blinded starter supplies are available for this protocol.

Important information for drug orders:

At the time of randomization each patient will be assigned a patient specific Blinded Drug ID number, example DR1117. The Blinded Drug ID number will appear on the patient's Confirmation of Registration Form.

The E2212 Drug Request Form must include the patient specific Blinded Drug ID number with each drug request in order for the drug order to be processed. Failure to provide this information on the drug order form will result in a delay of the drug order being processed and shipped.

This study is a double-blinded treatment protocol. Blinded blister packs of everolimus and matching placebo MAY NOT be transferred from one patient to another patient.

Each shipment will contain a 3-month supply of everolimus/placebo. Study drug is provided in blister packs. Each blister pack contains 10 5 mg tablets.

Institutions should allow 4 business days for receipt of the everolimus/placebo from the date the drug request is received by UVI. Shipments will be made from UVI Monday through Thursday for delivery onsite Tuesday through Friday.

There will be no weekend or holiday delivery of drugs.

Reorders: Institutions should keep in mind that shipments take 4 business days from the date the drug request is received by the ECOG-ACRIN Drug Team. Reorders using the E2212 Drug Request Form should be emailed to the ECOG-ACRIN Drug Team at 900.drugorder@jimmy.harvard.edu.

Each shipment will contain a 3-month supply of everolimus/placebo. Study drug is provided in blister packs. Each blister pack contains 10 5 mg tablets.

Once approved by the ECOG-ACRIN Drug Team, the drug will be received on site within 4 business days. Shipments will be made from UVI, Inc. Shipments will be made from UVI Monday through Thursday for delivery onsite Tuesday through Friday.

There will be no weekend or holiday delivery of drugs.

8.1.2 Drug Inventory Records

Investigational Product Records at Investigational Site(s): It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines.

8.1.3 Drug Destruction

At the completion of the patient's treatment at your institution, all unused drugs, partially used, or empty blister packs must be destroyed at the site according to the institution's policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities.

8.1.4 Emergency Unblinding

The information provided below is for the use by a physician, nurse, CRA or pharmacist treating the patient. These contact numbers should not be used by patients. Patients should be instructed to call their doctor's office in the event of an emergency or adverse event that may result in the need to unblind the patient.

In the event of an emergency or severe adverse reaction necessitating identification of the medication for the welfare of the patient, please contact the Study Chair, Dr. Steven Libutti M.D.,- at 718-920-4231 or Email slibutti@montefiore.org, first to ensure the reason for unblinding is valid. Then call a member of the ECOG-ACRIN Operations Office – Boston drug team at (617) 632-3610 Monday through Friday between 9:00 AM and 5:00 PM Eastern Time. For unblinding outside of these hours, contact AnswerConnect at 1-866-296-8940. This service will request the reason for unblinding and then page the on-call ECOG-ACRIN staff who will return your call and provide the unblinded treatment assignment if applicable. Remember, AnswerConnect should only be contacted outside of normal business hours and only in the event of an emergency. The ECOG-ACRIN Operations Office – Boston or AnswerConnect will require the protocol

number (i.e., “E2212”), the patient ID number (e.g., “44444”), and the patient initials (e.g., “FL”) to unblind the patient. Note that if a patient is unblinded, he/she must discontinue protocol treatment.

8.1.5 **Other Names**

Afinitor

8.1.6 **Classification**

mTOR inhibitor

8.1.7 **Mode of Action**

Everolimus acts as an inhibitor of cytokine and growth-factor-dependent proliferation of cells. Currently, the only known target of everolimus is mTOR, a key regulatory protein affecting various cell functions including cell proliferation(22). Everolimus exerts its activity through high affinity interaction with FKBP12. The FKBP12/everolimus complex subsequently interacts with the mTOR protein kinase, inhibiting downstream signaling events involved in regulation of the G1 to S-phase transition.

8.1.8 **Storage and Stability**

Store everolimus/placebo tablets at 25°C (77°F); excursions permitted between 15° – 30°C (59° – 86°F). See USP Controlled Room Temperature. Store in the original container, protect from light and moisture. Keep this and all drugs out of the reach of children.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.

Everolimus/placebo tablets should not be crushed. Do not take tablets which are crushed or broken.

Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient. The storage conditions for everolimus/placebo will be described on the medication label.

Tablets are blister-packed under aluminum foil, which should be opened only at the time of administration as drug is both hygroscopic and light-sensitive.

8.1.9 **Dose Specifics**

The recommended dose of everolimus/placebo for treatment of advanced PNET is 10 mg, to be taken once daily.

8.1.10 **Preparation**

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

8.1.11 Route of Administration

Everolimus/placebo should be administered orally once daily at the same time every day, either consistently with food or consistently without food.

8.1.12 Incompatibilities

Agents that may Increase Everolimus/Placebo Blood Concentrations:

CYP3A4 Inhibitors and PgP Inhibitors: See Appendix V for a list of CYP3A4 inhibitors.

In healthy subjects, compared to everolimus treatment alone there were significant increases in everolimus/placebo exposure when everolimus/placebo was coadministered with:

- ketoconazole (a strong CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 3.9- and 15.0-fold, respectively.
- erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 2.0- and 4.4-fold, respectively.
- verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 2.3- and 3.5-fold, respectively.

Concomitant strong inhibitors of CYP3A4 should not be used

Use caution when everolimus is used in combination with moderate CYP3A4 and/or PgP inhibitors.

Agents that may Decrease Everolimus/Placebo Blood Concentrations:

CYP3A4 Inducers:

In healthy subjects, co-administration of everolimus/placebo with rifampin, a strong inducer of CYP3A4, decreased everolimus/placebo AUC and Cmax by 63% and 58% respectively, compared to everolimus/placebo treatment alone. Consider a dose increase of everolimus/placebo when co-administered with strong CYP3A4 inducers if alternative treatment cannot be administered. St. John's Wort may decrease everolimus/placebo exposure unpredictably and should be avoided. See Appendix V for a list of CYP3A4 inhibitors.

Agents whose Plasma Concentrations may be Altered by Everolimus/Placebo:

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between everolimus/placebo and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of everolimus.

Coadministration of everolimus/placebo and depot octreotide increased octreotide Cmin by approximately 50%.

Immunosuppressants may affect the response to vaccination and vaccination during treatment with everolimus may therefore be less effective. The use of live vaccines should be avoided during treatment

with Everolimus. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

8.1.13 **Side Effects**

Information about common side effects already known about the investigational drug can be found in the Investigators' Brochure.

8.1.13.1 Gastrointestinal disorders:

- Stomatitis
- Diarrhea
- Abdominal pain
- Nausea
- Vomiting
- Constipation
- Dry mouth

8.1.13.2 General disorders and administration site conditions:

- Fatigue/malaise
- Edema (general and peripheral)
- Fever
- Asthenia

8.1.13.3 Infections and infestations

- Nasopharyngitis/rhinitis/URI
- Urinary tract infection

8.1.13.4 Investigations

- Weight decreased

8.1.13.5 Metabolism and nutrition disorders

- Decreased appetite
- Diabetes mellitus

8.1.13.6 Musculoskeletal and connective tissue disorders

- Arthralgia
- Back pain
- Pain in extremity
- Muscle spasms

8.1.13.7 Nervous system disorders

- Headache/migraine
- Dysgeusia
- Dizziness

8.1.13.8 Psychiatric disorders

- Insomnia

8.1.13.9 Respiratory, thoracic and mediastinal disorders

- Cough/productive cough
- Epistaxis
- Dyspnea/dyspnea exertional
- Pneumonitis
- Oropharyngeal pain

8.1.13.10 Skin and subcutaneous disorders

- Rash
- Nail disorders
- Pruritus/pruritus generalized
- Dry skin/xeroderma

8.1.13.11 Vascular disorders

- Hypertension

8.1.13.12 Laboratory abnormalities

- Anemia
- Thrombocytopenia
- Lymphopenia
- Neutropenia
- LFT derangement
- Renal function abnormality
- Hypercholesterolemia

8.1.14 **Nursing/Patient Implications**

- Non-infectious Pneumonitis

  Warn patients of the possibility of developing non-infectious pneumonitis. In clinical studies, some non-infectious pneumonitis cases have been severe and occasionally fatal. Advise patients to report promptly any new or worsening respiratory symptoms.

- Infections

  Inform patients that they are more susceptible to infections while being treated with everolimus/placebo and that cases of hepatitis B reactivation have been associated with everolimus/placebo treatment. In clinical studies, some of these infections have been severe (e.g., leading to respiratory or hepatic failure) and occasionally fatal. Patients should be aware of the signs and symptoms of infection and should report any such signs or symptoms promptly to their physician.

- Oral Ulceration

  Inform patients of the possibility of developing mouth ulcers, stomatitis, and oral mucositis. In such cases, mouthwashes and/or topical treatments are recommended, but these should not contain alcohol or peroxide.

- Renal Failure Events

  Inform patients of the possibility of developing kidney failure. In some cases kidney failure has been severe and occasionally fatal. Inform patients of the need for the healthcare provider to monitor kidney function, especially in patients with risk factors that may impair kidney function.

- Laboratory Tests and Monitoring

  Inform patients of the need to monitor blood chemistry and hematology prior to the start of everolimus/placebo therapy and periodically thereafter.

- Drug-drug interactions

  Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications and dietary supplements. Avoid concurrent treatment with strong CYP3A4 inhibitors. Use caution if everolimus/placebo must be co-administered with moderate CYP3A4 and/or PgP inhibitors; reduce the dose and carefully monitor the patient for undesirable effects. Avoid concurrent treatment with strong CYP3A4 inducers. If everolimus/placebo must be co-administered with strong CYP3A4 inducers, consider a dose increase and carefully monitor the patient for clinical response.

  Patients should avoid eating grapefruit and citrus fruits or drinking their juices while in the study. The juices in these fruits can change the way the body treats or breaks down everolimus (Afinitor®).

- Hepatic Impairment

  Advise patients that everolimus/placebo is not recommended in patients with severe hepatic impairment (Child-Pugh class C). For advanced PNET and advanced RCC patients with moderate hepatic impairment (Child-Pugh class B), prescribe a reduced dose of 5 mg everolimus per day. For SEGA patients with moderate hepatic impairment (Child-Pugh class B), adjustment to the starting dose may not be needed. However, subsequent dosing should be individualized based on therapeutic drug monitoring.

- Vaccinations

  Advise patients to avoid the use of live vaccines and close contact with those who have received live vaccines.

- Pregnancy

  Advise female patients of childbearing potential and sexually active males that everolimus/placebo may cause fetal harm and that a highly effective method of contraception or abstinence must be used during therapy with everolimus/placebo and for 8 weeks after ending treatment.

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

stopping treatment. Highly effective contraception is defined as either:

- Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]
- Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female subjects on the study, the vasectomised male partner should be the sole partner for that subject].
- Use of a combination of any two of the following (a+b or a+c or b+c):
  a. Use of oral, injected, implanted or other hormonal methods of contraception
  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

In case of use of oral contraception, women should have been stable on the oral agent before taking study treatment.

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

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

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

- Dosing Instructions

  Inform patients to take everolimus/placebo orally once daily at the same time every day, either consistently with food or consistently without food. The tablets should not be crushed or chewed. Everolimus/placebo should be swallowed whole with a glass of water. For patients unable to swallow tablets, everolimus/placebo tablet(s) should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring, immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse should be completely swallowed to ensure that the entire dose is administered.

If vomiting occurs, no attempt should be made to replace the vomited dose.

Instruct patients that if they miss a dose of everolimus/placebo, they may still take it up to 6 hours after the time they would normally take it. If more than 6 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take everolimus/placebo at the usual time. Warn patients to not take 2 doses to make up for the one that they missed.

8.1.15 References

22. Boulay A, Lane HA. The mammalian target of rapamycin kinase and tumor growth inhibition. Recent Results Cancer Res. 2007;172:99-124.

9. Statistical Considerations

Endpoints

Primary endpoint: Disease free survival

Secondary endpoints: Overall survival

The definitions of primary and secondary endpoints are described in Section 9.3.

Sample size with power justification

The trial will be a randomized double-blinded, placebo-controlled Phase II design with patients equally randomized between everolimus (Arm A) or placebo (arm B.) Randomization will be stratified on the factors outlined in Section 4. A total of 150 patients will be needed to accrue 144 randomized eligible cases. The study seeks to establish an improvement in the primary endpoint, which is defined as an 80% increase in median disease-free survival (DFS) from 15 months in the control arm (Arm B) to 27 months in the experimental arm (Arm A). The study is designed to have 90% power for a 44% reduction in the hazard rate with 144 eligible patients and 82 DFS events (as total information) which are expected to occur with 38 months of accrual at 4 patients per month and 7 additional months of follow-up, using a log-rank test at a one–sided significance level of 0.10. Under exponential distributions the hypothesized reduction corresponds to the improvement in median DFS from 15 months to 27 months and 3-year disease-free survival of 39.7% in Arm A versus 18.9% in Arm B. The sample size was computed using seqopr6 (part of the study design library at the ECOG-ACRIN Statistical Office).

Analysis plan including plans for formal interim analysis

The primary analysis set will include all randomized eligible patients. Disease-free survival (DFS) is defined as time from randomization to the earlier of documented recurrence (a return of tumor imaged by CT or MRI, new invasive primary cancer, or death without recurrence). Patients alive without documented recurrence or secondary primary reported will be censored at the time of the last documented disease evaluation. Tumor recurrence will be evaluated using evaluation criteria defined in Section 6 for a return of tumor imaged by CT or MRI. In the secondary analyses, overall survival (OS) is defined as time from randomization to death from any cause, censoring cases who are alive at the date of last contact. Kaplan-Meier estimates will be used for event-time distributions. DFS and OS by arm will be compared using one-sided stratified log-rank tests. Cox's proportional hazards models will be used to estimate hazard ratios. Toxicity will be assessed through summaries of adverse events by arm. Formal comparison of toxicity rates between the arms is not a goal of this trial and the sample size will provide sufficient power for detecting only relative large difference in adverse events. With 75 patients per arm, the study will have sufficient precision to provide 90% confidence interval on toxicity that will be no wider than 20%. For rare toxicities with 2% true probability, there will be 78% probability of observing one or more toxicities in either treatment arm. For rare toxicities with 3% true probability, there will be 90% probability of observing one or more toxicities on either treatment arm. Patient demographics and disease characteristics will be compared using two-sample t-tests or Fisher's exact tests

with a two-sided significance level of 0.10 as appropriate. Stratification will be used to ensure balance between groups and not for subset analysis.

The study will be monitored for potential efficacy stopping using an early look at DFS after approximately 50% of the planned full information (41/82 DFS events) has been observed. A one-sided log-rank test for DFS will be performed for the monitoring analysis. To preserve the overall type I error rate at 0.10, a critical value at the interim analysis will be determined using the O'Brien-Fleming boundary. Under the planned accrual schedule with four patients per month (3.8 eligible patients/ month), the monitoring analysis is projected to occur at 28.3 months following the start of accrual. If the true control median DFS is 15 months and the true experimental median DFS is 27 months, there will be 42% probability of crossing the upper efficacy boundary (2.05).

This study will also be monitored for futility using a rule that the study will be stopped early for lack of benefit if the estimated hazard ratio for experimental/control ≥ 1 at 50% of the planned full information. There will be 50% probability of early termination under the null hazard ratio of 1.0 (experimental/control) and 3.6% probability of early termination under the target alternative hazard ratio of 0.56 (experimental/control).

Safety Monitoring

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.2.

Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Office - Boston.

Gender and Ethnicity

Based on data from E6201 the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	3	3	6
Not Hispanic or Latino	66	78	144
Ethnic Category: Total of all subjects	**69**	**81**	**150**

Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	1	1	2
Black or African American	5	5	10
Native Hawaiian or other Pacific Islander	0	0	0
White	63	75	138
Racial Category: Total of all subjects	**69**	**81**	**150**

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

10. Specimen Submissions

Fixed paraffin-embedded metastatic tumor from core biopsy or surgery must be submitted for central diagnostic review and classification. Primary tumor tissue, if available, is also requested. Blood specimens and frozen tissue, if available, are to be submitted for use in research from consenting patients. Descriptions of the diagnostic review and examples of potential research studies are in Section 11.

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SAMPLE TRACKING SYSTEM (STS): All specimens submitted on this trial must be entered and tracked using the ECOG-ACRIN Sample Tracking System. Any case reimbursements associated with specimen submissions to ECOG-ACRIN–designated laboratories will be determined only from data contained in STS.

LABELING: Specimens are to be labeled clearly with the ECOG-ACRIN protocol number "E2212", patient initials, date and time of collection, and sample type. All sample submissions are to be accompanied with an STS shipping manifest.

SHIPPING ACCOUNT: Samples shipped to the ECOG-ACRIN PCORL or Libutti Laboratory are to be shipped using the PCORL's FedEx account using the FedEx On-Line Services. Access to the shipping account for specimen shipments to the ECOG-ACRIN PCORL at Northwestern University can now only be obtained by logging into fedex.com with an account issued by the ECOG-ACRIN PCORL. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN PCO by email at ecogpcorl@northwestern.edu

Submissions to the (PCORL) - MANDATORY

The ECOG-ACRIN Pathology Coordinating Office-Reference Laboratory (PCORL) is the receiving laboratory for all specimens submitted from patients participating in this trial.

10.1.1 Pathology Materials - MANDATORY

Submission of pathology materials from all patients is **mandatory**. The submitting pathologist and clinical research associate should refer to Appendix I (Pathology Submission Guidelines) for guidelines and summary of submission requirements. Failure to submit the required materials may render the patient's data unevaluable.

The required materials are to be submitted within four (4) weeks following randomization.

If these criteria cannot be met, please contact the ECOG-ACRIN Pathology Coordinating Office (PCO) (ecogpcorl@northwestern.edu) to obtain alternative submission requirements.

A. FFPE TUMOR TISSUE

All of the following materials are to be submitted. If unavailable, please contact the PCORL and provide justification in STS.

- All original stained diagnostic slides.

  NOTE: These slides will be returned to the site upon completion of the review which is retrospective and will be performed in batches. If the return of

these slides is to be expedited, please indicate as such in the appropriate comment field in STS.

- One representative diagnostic-fixed paraffin-embedded **metastatic liver tumor block,** core biopsy or surgical specimen.
- One representative diagnostic fixed paraffin-embedded **primary tumor block**, core biopsy or surgical specimen, if available.

NOTE: If blocks are not available for submission, submit the following:

- Two (2) H&E slides.
- Twenty (20) unstained charged slides 4 or 5 µm thick
- Two (2) 4mm cores.

B. FORMS

- Pathology Material Submission Form (#638 v04.2), Parts A & B completed. Please identify the clinical status of the submitted materials
- A copy of the surgical (if appropriate) and pathology reports
- Immunologic studies, if available
- Sample Tracking System Shipping Manifest

10.1.2 Specimens from Consenting Patients

Specimens are to be submitted from patients who answered "yes" to *"I agree to provide additional samples for research."*

Blood specimens are to be collected prior to start of treatment and upon completion/end of treatment. The pretreatment samples, ideally, are to be drawn at 6-8 WEEKS POST-SURGERY, prior to start of protocol therapy. If protocol treatment will begin prior to the sixth week post-surgery, still collect prior to start of treatment.

Institution supplies are to be used for the collection and shipment of blood and frozen tissue specimens. No kits are available.

Blood samples are to be frozen (at < -70ºC) as quickly as possible after draw. If samples are frozen in a standard freezer (approximately -20ºC), it is asked that samples be shipped within a month of collection.

Questions are to be directed to the ECOG-ACRIN PCORL (ecogpcorl@northwestern.edu), Dr. Steven Libutti, Phone: (718) 920-4231, FAX: (718) 798-0309, E-mail: slibutti@montefiore.org.

A. Frozen Surgical Tumor Tissue Specimens

Specimens are to be shipped overnight with the blood specimens on dry ice.

The site's pathology ID for submitted frozen tissue samples must be provided in STS. If samples are not available, indicate as such in the STS as well. This information will reduce unnecessary follow-up with the site by the laboratory.

B. Peripheral Blood, ACD vacutainer

Draw prior to start of protocol therapy, ideally 6-8 weeks post-surgery.

- Draw blood into a 10 mL ACD vacutainer (EDTA tube may substitute). Invert gently eight to ten times to thoroughly mix the blood and anti-coagulant.
- Specimens collected in glass vacutainers must be transferred to sterile cryovials prior to freezing. Plastic vacutainers may be frozen directly. Freeze at ≤ -70ºC until shipped

C. Plasma, EDTA (purple top)

Draw prior to start of protocol therapy, ideally 6-8 weeks post-surgery.

- Draw peripheral blood into vacutainer and gently invert 8-10 times.
- Within 20 minutes of collection, centrifuge at 1500xg (2700-3000 rpm) for 15 minutes.
- Pipette the plasma into **4 cryotubes** (approximately 1 mL each) and store frozen, below –20ºC (-70 ºC preferred), until shipped
- Remaining Cells: If the vacutainer is plastic, replace the stopper on the EDTA tube containing the cells and ship with the plasma samples.

10.1.3 Shipping Guidelines

The receiving laboratory is not available to receive shipments over holidays or weekends. Therefore, samples are only to be shipped via overnight courier Sunday through Thursdays (excluding a day before a holiday).

The required initial diagnostic tumor tissue materials, reports and forms are to be submitted within four (4) weeks following patient randomization.

Frozen samples are to be shipped on dry ice (5 lbs. minimum). Samples batched in a regular freezer are to be shipped within a month following the draw. Samples stored at < -70ºC may be shipped on a quarterly basis.

Samples from multiple patients may be batched and shipped together. All samples must be adequately labeled with protocol number, ECOG-ACRIN patient case number, and date of collection.

Shipping Address

ECOG-ACRIN Pathology Coordinating Office
Robert H. Lurie Comprehensive *Cancer Center of* Northwestern University Medical School
Olson Pavilion - Room 8421
710 North Fairbanks Court
Chicago, IL 60611
Tel: (312) 503-3384
FAX: (312) 503-3385

Tissue specimens shipped standard mail must utilize a "trackable" mechanism. For shipments utilizing FedEx, access to the shipping account for specimen shipments requires logging into fedex.com with an account issued by the ECOG-ACRIN PCORL.

ECOG-ACRIN Sample Tracking System

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Important: Any case reimbursements associated with specimen submissions will not be credited if specimens are not logged into STS. Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to .

Study Specific Notes

Generic Specimen Submission Form (#2981v2) will be required only if STS is unavailable at time of sample submission. Include site contact information on the form. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory the day of shipping. Indicate the shipping tracking number and the appropriate Lab ID# on the submission form:

- 0001 = ECOG-ACRIN PCORL

Retroactively enter all specimen collection and shipping information when STS is available.

Use of Specimens in Research

Tissue specimens will be processed and distributed to investigators for the central diagnostic review.

Specimens from patients who consented to allow their specimens to be used for research studies will be retained in an ECOG-ACRIN-designated central repository. For this trial, specimens will be retained at the ECOG-ACRIN Pathology Coordinating Office.

Specimens submitted will be processed to maximize their utility for current and future research projects. Processing may include, but not limited to, extraction of DNA and RNA and construction of tissue microassays (TMAs). DNA and plasma (if appropriate) will be isolated from the submitted peripheral blood samples.

Any residual blocks will be available for purposes of individual patient management on specific written request.

Request for the use of archived specimens requires submission of a correlative science proposal detailing the scientific hypothesis, research plan, assay methods for use of the biospecimens, and a complete statistical section (with adequate power justification and analysis plan) will be submitted and reviewed by CTEP in accordance with the NCI National Clinical Trials Network (NCTN) review policies.

If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study. Bloods and other products may be destroyed per protocol of the given lab, or they could be anonymized (stripped of all identifiers) and used for instrument calibration or other quality control measures which are not published or linked to the clinical trial. Tissue will be returned or stored indefinitely in for return to the site upon request.

Sample Inventory Submission Guidelines

Inventories of all samples submitted from institutions will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized for approved laboratory research studies will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office – Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office – Boston.

11. Laboratory Research Studies

Diagnostic Review and Classification (MANDATORY)

Central pathological review will include Ki-67 and mitotic index, NANETS grading system will be employed (19, 20). The review will be performed by Dr. Guang-Yu Yang at Northwestern University. The analysis will be retrospective and will be used for determination of patient evaluability. The results of the review will not impact patient participation in the trial.

Research Studies

Blood and tumor specimens are requested from consenting patients for future research studies. Request for the use of archived specimens, via a protocol amendment or a separate correlative science proposal, will be in accordance with the ECOG-ACRIN and NCI National Clinical Trials Network (NCTN) policies.

The background supporting the following potential research studies is presented in the introduction of this protocol. These studies, if performed, will be performed under the direction of Drs. Steven Libutti, Montefiore Medical Center, and Luis Diaz, Johns Hopkins University.

11.2.1 Predictive value of PIK3CA, PTEN, and TSC Mutations

We hypothesize that patients with tumors that are mutant for PIK3CA, PTEN or TSC will benefit in terms of DFS and OS as compared to patients with tumors without mutations in these genes.

DNA from tumor tissue and germline DNA from peripheral blood will be used for these studies.

Sequencing will be performed following PCR amplification of the regions of interest. Mutations detected will be confirmed using the tumor and matched normal DNA (obtained from whole blood).

Mutations identified in the tumor will be used to design primers and probes to detect circulating tumor DNA (ctDNA) fragments that contain these mutations using highly sensitive PCR-based methodologies (i.e. BEAMing or SafeSeqs) (see below).

11.2.2 Analysis of post-operative circulating tumor DNA to detect minimal residual disease and predict disease recurrence

We hypothesize that the post-operative detection of ctDNA is consistent with the presence of minimal residual disease and signifies a population of patients that will suffer with disease recurrence.

DNA extracted from plasma from each time point collected will be interrogated for the presence of ctDNA using probes designed from mutations detected in the tumor tissue (see above). At this time, the proposed genomic method to detect and quantify the ctDNA,“BEAMing”, is described in the introduction to the protocol.

11.2.3 Mutations in Chromatin Remodeling Genes

We hypothesize that tumors with defect in chromatin remodeling will confer a survival benefit to patients with metastatic pancreatic tumors.

Sequencing of DAXX, ATRX and MEN1 will be performed following PCR amplification of the regions of interest. Mutations detected will be confirmed using the tumor and matched normal DNA (obtained from whole blood).

Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secured data transfer to the ECOG-ACRIN Operations Office – Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the investigator. The quarterly cut-off dates are March 31, June 30, September 30, and December 31. Data is due at the ECOG-ACRIN Operations Office – Boston 1 week after these cut-off dates.

12. Electronic Data Capture

Please refer to the E2212 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31st.

Records Retention

This study is being conducted under an IND exemption and is not intended to support any FDA-related filings. However, ECOG-ACRIN requires clinical investigators to retain all trial-related documentation, including source documents, for at least one year from the posting of the final clinical study report of the outcome of this trial to support any publication of the data. Please contact the ECOG-ACRIN Operations Office – Boston prior to destroying any source documents.

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

14. References

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A Randomized, Double-Blinded, Placebo-Controlled Phase II Study of Adjuvant Everolimus Following the Resection of Metastatic Pancreatic Neuroendocrine Tumors to the Liver

Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. List of Required Materials for E2212
4. Pathology Submission Form (#638 v04.2)

Guidelines for Submission of Pathology Materials

E2212: A Randomized, Double-Blinded, Placebo-Controlled Phase II Study of Adjuvant Everolimus Following the Resection of Metastatic Pancreatic Neuroendocrine Tumors to the Liver

The following materials are to be submitted within one month of randomizing patient to the trial

1. Pathology materials required for pathology review and, per patient consent, research
   - REQUIRED FOR CENTRAL DIAGNOSTIC REVIEW
     - One representative diagnostic-fixed paraffin-embedded **metastatic tumor block,** core biopsy or surgical specimen.
     - One representative diagnostic fixed paraffin-embedded **primary tumor block**, core biopsy or surgical specimen, if available
     - Original stained diagnostic slides

       NOTE: These slides will be returned to the site upon completion of the review which is retrospective and will be performed in batches. If the return of these slides is to be expedited, please indicate as such in the appropriate comment field in STS.
   - If available, frozen surgical tumor tissue
2. Forms and reports:

   The following items are to be included with every submission of pathology materials.
   - Institutional Surgical Pathology Report
   - Pathology Material Submission Form (#638 v04.2) – Parts A & B completed
   - ECOG-ACRIN Sample Tracking System (STS) manifest

   NOTE: Adequate patient identifying information must be included with every submission. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials, will expedite any required communications with the institution (including site pathologists).
3. Mail pathology materials to:

   ECOG-ACRIN Pathology Coordinating Office
   Robert H. Lurie Comprehensive Cancer Ctr
   of Northwestern University Medical School
   Olson Pavilion - Room 8421
   710 North Fairbanks Court
   Chicago, IL 60611

   If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Pathology Coordinating Office at (312) 503-3384 or FAX (312) 503-3385 or ecogpcorl@northwestern.edu.

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD
Group Co-Chairs

MEMORANDUM

TO: (Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Pathology Committee

DATE:

SUBJECT: Submission of Pathology Materials for E2212: *A Randomized, Double-Blinded, Placebo-Controlled Phase II Study of Adjuvant Everolimus Following the Resection of Metastatic Pancreatic Neuroendocrine Tumors to the Liver*

The patient named on the attached Pathology Material Submission Form (#638 v04.2) has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for diagnostic review and research studies.

Please complete PART B of the Submission Form. Keep a copy for your records and return the completed Submission Form, the surgical pathology report(s), the slides and/or blocks and any other required material (see List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the appropriate laboratory.

Pathology materials submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies per patient consent. Paraffin blocks will be returned upon request for purposes of patient management.

Please note: Since blocks are being used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.

Results of the diagnostic review will be distributed to you upon completion of the review. This review will be retrospective and will not impact patient participation in E2212.

If you have any questions regarding this request, please contact the Pathology Coordinating Office at (312) 503-3384 or FAX (312) 503-3385.

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address: _____

Phone: _____

Thank you.

Form No. 638 v04.2 **ECOG DIAGNOSTIC PATHOLOGY MATERIAL SUBMISSION FORM**

Instructions: **This form is a required part of pathology submission.** Please complete and submit along with all pathology material and corresponding pathology reports requested by the protocol. See list of required materials as specified in EACH protocol.

ECOG PCO-RL IS FULLY- COMPLIANT WITH DHHS, HIPAA, AND OHRP REGULATIONS Tel. **312-503-3384**
Fax 312-503-3385

PART A: To Be Completed By Data Manager/CRA

DO NOT USE INITIALS – Submit Patient's FULL Name
(The Patient has authorized the use of PHI.)

Date sample sent to ECOG _____/_____/_____ (M,D,Y)
Data Manager_____
Address _____
_____
Telephone No. ( ) _____
Fax No. ( ) _____
Email address _____

Patient's Name:
Last_____ First _____
ECOG Prot. No. _____ ECOG Patient Seq. No. _____
Participating Group Prot. No. _____ Participating Group Patient ID No._____
Group _____ Institution_____ PI_____
Step No. _____ Affiliate _____
ECOG Parent Prot. No. _____ Seq. No._____

PART B: TO BE COMPLETED BY DATA MANAGER/CRA AND SUBMITTING PATHOLOGIST

	Status* (See Below)	Date Specimen Collected (M/D/Y)	Disease Site	Number of Slides/Vials	Specimen ID Numbers	Type of Stain	PCO-RL Use Only: PCO ID Numbers
Complete for Slides/Vials		/ /					
		/ /					
	Status* (See Below)	**Date Specimen Collected (M/D/Y)**	**Disease Site**	**Number of Blocks/Punch**	**Specimen ID Numbers**	**Fixative**	**PCO ID Numbers**
Complete for Blocks/Punch		/ /					
		/ /					

***Status:** Please identify the clinical status of the sample.
List ***all*** that apply:

1. Original diagnostic material
2. AML/MDS diagnosis
3. Pre-protocol treatment biopsy/tissue
4. Post-protocol treatment biopsy/tissue
5. Post-surgery biopsy/tissue
6. Relapse/recurrence
7. Remission/response
8. Other, specify: _____

Submitting Pathologist _____
Telephone No. ( ) _____
Address _____
_____

Did the patient consent to participate in the storage of samples for future research? Yes No

MATERIAL RETURN (All materials will be retained by the ECOG PCO unless return is requested here.)

Does the submitting institution's policy require the return of any submitted material (blocks, H&E slides, etc.)? Yes No

If so, please indicate which materials must be returned _____

All materials will be returned to the **submitting pathologist** unless an alternate address is indicated here _____

If materials were not able to be submitted for this protocol and its correlative studies, please circle the reason for non-submission. Attach a formal letter referencing regulations, policy, and/or other explanation. If possible, include a copy of the policy.

Federal/State Regulations ____ Hospital/Institutional Policy _____ Insufficient Tissue _____ Other_____ (Specify) _____

Pathologist of Investigator's Signature _____

(PCO-RL Use Only)
PV _____

PART C: ECOG PATHOLOGY COORDINATING OFFICE USE ONLY

Date Sample Received at PCO ____/____/____ Date Sent to Reviewer ____/____/____ Date Sent to PI/Central Lab ____/____/____

Site Compliance %_____ Name of Reviewer_____ PI/Central Lab_____

PCO Comments: _____ Staff Init. _____

Investigator: Keep a copy for your files and submit original form to the destination specified in protocol. 2/05

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Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we will improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the ECOG-ACRIN Cancer Research Group, with the participation of people like you in clinical trials, we thank you again.

Sincerely,

[PHYSICIAN NAME]

A Randomized, Double-Blinded, Placebo-Controlled Phase II Study of Adjuvant Everolimus Following the Resection of Metastatic Pancreatic Neuroendocrine Tumors to the Liver

Appendix III

Patient Tablet Calendar

Tablet Calendar Directions

1. Take your scheduled dose of each tablet as instructed by your doctor.
2. If you forget, the missed tablets will not be taken if more than six hours late.
3. Note the time and number of tablets you take each day. If you develop any side effects or symptoms, please record them in the appropriate spot on your calendar. If you take any medications other than everolimus/placebo, note them in the appropriate spot on your calendar.
4. Please bring the bottle, any leftover tablets, and your tablet calendar to your next clinic visit.

Patient Tablet Calendar

Patient ID #: _____ **Drug Name:** Everolimus/Placebo

Dose: _____ **Cycle#:** _____

DAY	Date Month	Day	Year	Time tablets taken	Number of tablets taken	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
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26						
27						
28						
29						
30						

Additional Notes:

Patient signature: _____ **Date:** _____

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Appendix IV

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

A Randomized, Double-Blinded, Placebo-Controlled Phase II Study of Adjuvant Everolimus Following the Resection of Metastatic Pancreatic Neuroendocrine Tumors to the Liver

Appendix V

Drugs Which May Affect Everolimus Metabolism

The following is a list of common CYP3A4 inducers and inhibitors which may impact everolimus metabolism. This is NOT a complete list of medications potentially incompatible with everolimus; therefore patient medications must be evaluated closely to determine patient eligibility for this trial.

List of CYP3A4 Inducing Agents:

Carbamazepine
Dexamethasone
Ethosuximide
Glucocorticoids
Griseofulvin
Modafinil
Naficillin
Nelfinavir
Nevirapine
Oxcarbazepine
Phenobarbitol
Phenylbutazone
Phenytoin
Primidone
Progesterone
Rifabutin
Rifampin
Rifapentine
Rofecoxib
St. John's Wort
Sulfadimidine
Sulfinpyrazone
Tipranavir
Troglitazone

List of CYP3A4 Inhibitors:

Amiodarone
Cimetidine
Ciprofloxacin
Clarithromycin
Delavirdine
Diethyl-dithiocarbamate
Diltiazem
Erythromycin
Fluconazole
Fluvoxamine
Gestodene
Grapefruit or Grapefruit juice
Indanvir
Itraconazole
Ketoconazole
Mibefradil
Mifepristone
Nefazodone
Nelfinavir
Norfloxacin
Norfluoxetine
Ritonavir
Roxithromycin
Saquinavir
Troleandomycin
Voriconazole
Warfarin
Amprenavir
Atazanavir
Miconazole
Telithromycin
Verapamil

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Rev. 5/14

Appendix VI

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on Everolimus/placebo, or within 28 days of the patient's last dose of Everolimus/placebo must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP's Adverse Event Reporting System (CTEP-AERS)

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm)

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERS report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERS report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status via CTEP-AERS.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office – Boston. Please contact the ECOG-ACRIN Operations Office – Boston to ask for a conference call to be set up with the appropriate individuals.
- It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an amendment to the initial CTEP-AERS report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a new CTEP-AERS report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the CTEP AEMD Help Desk at 301-897-7497 or aemd@tech-res.com, for it will need to be discussed on a case by case basis.

Reporting a Fetal Death

A fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

It must be reported via CTEP-AERS as Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions".

A fetal death should NOT be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

Reporting a Neonatal Death

A neonatal death is defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported via CTEP-AERS AND any infant death after 28 days that is suspected of being related to the in utero exposure to Everolimus/placebo must also be reported via CTEP-AERs .

It must be reported via CTEP-AERS as Grade 4 "General disorders and administration - Other (neonatal loss)"under the System Organ Class (SOC) "General disorder and administration".

A neonatal death should NOT be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

Additional Required Forms:

When submitting CTEP-AERS reports for pregnancy, pregnancy loss, or neonatal loss, the CTEP 'Pregnancy Information Form' must be completed and faxed along with any additional medical information to CTEP (301-230-0159). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

A Randomized, Double-Blinded, Placebo-Controlled Phase II Study of Adjuvant Everolimus Following the Resection of Metastatic Pancreatic Neuroendocrine Tumors to the Liver

Appendix VII

E2212 Drug Request Form

E2212 EVEROLIMUS/PLACEBO DRUG REQUEST FORM	
Section I (To be completed by the institution)	
CTEP NCI ID#:	
Principal Investigator:	
Institution Name:	
Institution Pharmacy Delivery Address:	
Pharmacy Contact:	
Pharmacy Contact Telephone Number:	
Pharmacy Contact email:	
Pharmacy Contact fax:	
Shipment Must Reach Destination By (Please allow 4 business days for delivery):	
ECOG-ACRIN Patient Sequence Number:	
Blinded Drug ID#:	
Initial Order or Resupply:	
Quantity of Blister Packs	

Order placed by: (print name)	**Signature:**	**Date:**

Section II (To be completed by ECOG-ACRIN Drug Team)		
IRB Approval: **Blinded Drug ID Confirmed:**		
Personnel Name:	**Signature:**	**Date:**

PLEASE EMAIL THIS DRUG REQUEST FORM AS AN ATTACHMENT TO 900.drugorder@jimmy.harvard.edu or by FAX: 617-632-2063

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Appendix VIII

Hepatitis Screening

Screening for hepatitis B

Prior to randomization, the following three categories of patients should be tested for hepatitis B viral load and serologic markers, that is, HBV-DNA, HBsAg, HBs Ab, and HBc Ab:

- All patients who currently live in (or have lived in) Asia, Africa, Central and South America, Eastern Europe, Spain, Portugal and Greece. [http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/hepatitis-b.htm]
- Patients with any of the following risk factors:
  - known or suspected past hepatitis B infection,
  - blood transfusion(s) prior to 1990,
  - current or prior IV drug users,
  - current or prior dialysis,
  - household contact with hepatitis B infected patient(s),
  - current or prior high-risk sexual activity,
  - body piercing or tattoos,
  - mother known to have hepatitis B
  - history suggestive of hepatitis B infection, e.g., dark urine, jaundice, right upper quadrant pain.
- Additional patients at the discretion of the investigator

Screening for hepatitis C

Prior to randomization, patients with any of the following risk factors for hepatitis C should be tested using quantitative RNA-PCR:

- known or suspected past hepatitis C infection (including patients with past interferon 'curative' treatment),
- blood transfusions prior to 1990,
- current or prior IV drug users,
- current or prior dialysis,
- household contact of hepatitis C infected patient(s),
- current or prior high-risk sexual activity,
- body piercing or tattoos.

At the discretion of the investigator, additional patients may also be tested for hepatitis C.