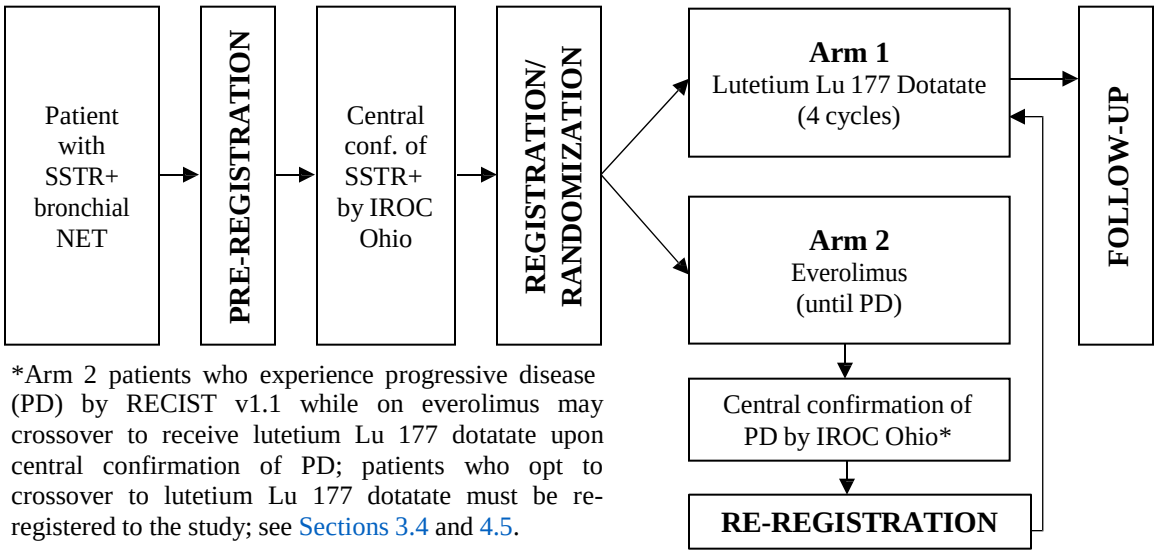
- Concurrent SSA use while on protocol therapy is allowed provided that the patient: 1) has a functional tumor, 2) has been on a stable dose of SSA therapy for at least three months, and 3) has previously demonstrated radiographic disease progression while on SSA therapy
- Concomitant treatment with ritonavir is not permitted on this study.
- Chronic concomitant treatment with strong inhibitors and/or inducers of CYP3A4 are not allowed on this study
- Chronic concomitant treatment with strong inhibitors and/or inducers of PgP are not allowed on this study

Re-registration Eligibility Criteria (see Section 3.4)

- Confirmation of disease progression by RECIST v1.1 by real-time Alliance ICL at IROC Ohio central radiographic review
- Not pregnant and not nursing
- ECOG Performance Status 0-2
- Required Laboratory Values as outlined in Section 3.4.4

Schema

Arm 1: One Cycle = 56 Days Arm 2: One Cycle = 28 Days



*Arm 2 patients who experience progressive disease (PD) by RECIST v1.1 while on everolimus may crossover to receive lutetium Lu 177 dotatate upon central confirmation of PD; patients who opt to crossover to lutetium Lu 177 dotatate must be re-registered to the study; see Sections 3.4 and 4.5.

Treatment with lutetium Lu 177 dotatate is to continue for a maximum of 4 cycles or until disease progression, unacceptable toxicity, or withdrawal of consent. Treatment with everolimus is to continue until disease progression, unacceptable toxicity, or withdrawal of consent. Patients will be followed for 5 years or until death, whichever comes first.

Arm 1 treatment will be administered at a CTEP and study authorized Targeted Radiopharmaceutical Facility (TRF). Arm 2 treatment will be administered at the registering institution. Follow-up (i.e. tests, observations, laboratory studies, imaging studies) after cessation of treatment may be performed at a non-registering institution.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply. All protocol conduct must be followed, and the registering institution is responsible for ensuring all data is reported per protocol.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

3.2 Pre-Registration Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

___ 3.2.1 Documentation of Disease

- **Pathologic Documentation:** Well- or moderately-differentiated neuroendocrine tumor(s) of bronchial origin (i.e. carcinoid) as assessed by local pathology.

  The pathology report must state ONE of the following: 1) well- or moderately-differentiated neuroendocrine tumor, 2) low- or intermediate-grade neuroendocrine tumor, or 3) carcinoid tumor (including typical or atypical carcinoid tumors).

  Documentation of histology from a primary or metastatic site is allowed.

  Functional (evidence of peptide hormones and/or bioactive substances associated with a clinical hormone syndrome such as carcinoid syndrome or Cushing's syndrome) or nonfunctional tumors are allowed.

  Patients with poorly-differentiated or high-grade neuroendocrine carcinoma (i.e. large cell neuroendocrine carcinoma of lung, small cell lung cancer) or mixed tumors (i.e. adenocarcinoid tumor) are not eligible.

- **Stage:** Recurrent or locally-advanced/unresectable or metastatic disease.
- **Tumor Site:** Neuroendocrine tumor of bronchial (i.e. lung) primary site.
- **Radiologic Evaluation:** Lesions must have shown radiological evidence of disease progression in the 12 months prior to pre-registration.

  Tumor must have shown somatostatin receptor (SSTR) positivity on ^{68}Ga-DOTATATE PET or other SSTR-PET scan in the 12 months prior to pre-registration; however, documentation of SSTR positivity in the 6 months prior to pre-registration is preferred. SSTR positivity is defined as uptake greater than background liver in all measurable lesions.

___ 3.2.2 Measurable Disease

Patients must have measurable disease per RECIST v1.1 by computer tomography (CT) scan or magnetic imaging (MRI); see Section 11.0. Any lesions which have undergone percutaneous therapies or radiotherapy should not be considered measurable unless the lesion has clearly progressed since the procedure.

Lesions must be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 1 cm with CT or MRI (or ≥ 1.5 cm for lymph nodes). Non-measurable disease includes disease smaller than these dimensions or lesions considered truly non-measurable including: leptomeningeal disease, bone metastases, ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung. See Section 11.0 for additional details.

3.3 Registration Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e. has had menses at any time in the preceding 12 consecutive months).

____ 3.3.1 Disease Status

Confirmation of SSTR positivity by Alliance ICL at IROC Ohio central radiographic review.

____ 3.3.2 Prior Treatment

Patients with treatment-naïve or previously-treated disease are allowed. Patients with previously-treated disease must have demonstrated radiographic disease progression on the prior therapy.

No prior treatment with peptide receptor radionuclide therapy (PRRT) (e.g. lutetium Lu 177 dotatate).

No prior treatment with mammalian target of rapamycin (mTOR) inhibitors (e.g. deforolimus, everolimus, sirolimus, temsirolimus, etc.).

Prior treatment with hepatic artery embolization (including bland embolization, chemoembolization, and selective radioembolization) or ablative therapies (i.e. cryoablation, radiofrequency ablation, etc.) is allowed if measurable disease remains outside of the treated area or if there is documented disease progression in a treated site. Prior liver-directed or other ablative treatment must be completed at least 28 days prior to registration.

Prior treatment with 90-Yttrium radioembolization must be completed at least 6 months prior to registration.

Radiation therapy (conventional fractionated or stereotactic ablative) to the lung and/or mediastinum must be completed at least 28 days prior to registration.

Prior treatment with systemic anticancer therapy must be completed **at least 28 days prior to registration** (except for somatostatin analogs in patients with functional tumors). Continuation of treatment with somatostatin analogs while on protocol therapy is allowed provided that the patient: 1) has functional tumors (evidence of peptide hormones and/or bioactive substances associated with a clinical hormone syndrome such as carcinoid syndrome or Cushing's syndrome), 2) has been on a stable dose of somatostatin analog therapy for at least three months, and 3) has previously demonstrated radiographic disease progression while on somatostatin analog therapy.

Patients must have completed any major surgery at least 28 days prior to registration. Complete wound healing from major surgery should occur prior to registration.

Patients should have improvement of any toxic effects of prior therapy (except alopecia, fatigue, and other non-reversible toxic effects such as neuropathy from cisplatin) to NCI CTCAE, version 5.0, grade 1 or less.

___ **3.3.3** Not pregnant and not nursing, because this study involves: 1) an investigational agent whose genotoxic, mutagenic, and teratogenic effects on the developing fetus and newborn are unknown, and 2) an agent that has known genotoxic, mutagenic, and teratogenic effects.

Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 14 days prior to registration is required.

___ 3.3.4 Age ≥ 18 years

___ 3.3.5 ECOG Performance Status 0-2

___ 3.3.6 Required Initial Laboratory Values:

Hemoglobin	≥ 8.0 g/dL
Platelet Count	≥ 75,000/mm^3
Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Creatinine	≤ 1.5 x upper limit of normal (ULN)
OR	
Calculated Creatinine Clearance	≥ 40 mL/min*
Total Bilirubin	≤ 2.0 x ULN**
Albumin	≥ 2.8 g/dL
AST/ALT	≤ 3.0 x ULN

*Calculated by the Cockcroft-Gault equation

**In patients with Gilbert's Syndrome, if total bilirubin is > 2.0 x ULN, then direct bilirubin must be ≤ 2.0 x ULN

___ 3.3.7 Comorbid Conditions

No known central nervous system metastases unless adequately treated, stable, and off steroid support for at least 14 days prior to registration.

No other currently active malignancy that requires therapy or is expected to require therapy during the study (excluding non-melanoma skin cancers or in situ carcinomas, such as breast or cervical).

No uncontrolled diabetes mellitus, defined as fasting glucose > 200 mg/dL, despite optimal medical therapy.

No known uncontrolled hypercholesterolemia (defined as fasting cholesterol > 300 mg/dL **OR** > 7.75 mmol/L) or hypertriglyceridemia (defined as fasting triglycerides > 2.5 x ULN), despite optimal medical therapy.

No known active hepatitis B (defined as HbsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected).

Patients with HIV positivity are allowed if CD4 Count > 500 cells/μL.

No known active or uncontrolled infections requiring ongoing antifungals or antibiotics in the 3 days prior to registration.

No receipt of live attenuated vaccines in the 7 days prior to registration.

No known liver cirrhosis.

No known prior drug-induced pneumonitis that was symptomatic or required treatment.

No known medical condition causing an inability to swallow and no known impairment of gastrointestinal function that may significantly alter the absorption of an oral agent.

No known hypersensitivity to everolimus or other rapamycin analogs (e.g. sirolimus, temsirolimus, etc.).

___ 3.3.8 Concomitant Medications

Concurrent somatostatin analog use while on protocol therapy is allowed provided that the patient: 1) has a functional tumor (evidence of peptide hormones and/or bioactive substances associated with a clinical hormone syndrome such as carcinoid syndrome or Cushing's syndrome), 2) has been on a stable dose of somatostatin analog therapy for at least three months, and 3) has previously demonstrated radiographic disease progression while on somatostatin analog therapy. For subjects receiving lutetium Lu 177 dotatate, there should be a minimum of 14 days between long-acting somatostatin analogue and lutetium Lu 177 dotatate dosing. Short-acting somatostatin analogs should not be administered within 24 hours of lutetium Lu 177 dotatate dosing. Following lutetium Lu 177 dotatate dosing, long-acting somatostatin analogs may be administered between 4 and 24 hours after each dose.

Chronic concomitant treatment with strong inhibitors or inducers of CYP3A4 is not allowed on this study. Patients on strong inhibitors or inducers of CYP3A4 must discontinue the drug(s) 7 days prior to registration; see Section 8.1.9 for more information.

Chronic concomitant treatment with strong inhibitors or inducers of P-glycoprotein (PgP) is not allowed on this study. Patients on strong inhibitors or inducers of PgP must discontinue the drug(s) 7 days prior to registration; see Section 8.1.10 for more information.

3.4 Re-registration Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e. has had menses at any time in the preceding 12 consecutive months).

___ 3.4.1 Disease Status

Confirmation of disease progression by RECIST v1.1 by real-time Alliance ICL at IROC Ohio central radiographic review.

___ 3.4.2 Not pregnant and not nursing.

Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 14 days prior to re-registration is required.

___ 3.4.3 ECOG Performance Status 0-2

___ 3.4.4 Required Laboratory Values:

Hemoglobin	≥ 8.0 g/dL
Platelet Count	≥ 75,000/mm^3
Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Creatinine	≤ 1.5 x upper limit of normal (ULN)
OR	
Calculated Creatinine Clearance	≥ 40 mL/min*
Total Bilirubin	≤ 2.0 x ULN**
Albumin	≥ 2.8 g/dL
AST/ALT	≤ 3.0 x ULN

*Calculated by the Cockcroft-Gault equation

**In patients with Gilbert's Syndrome, if total bilirubin is > 2.0 x ULN, then direct bilirubin must be ≤ 2.0 x ULN