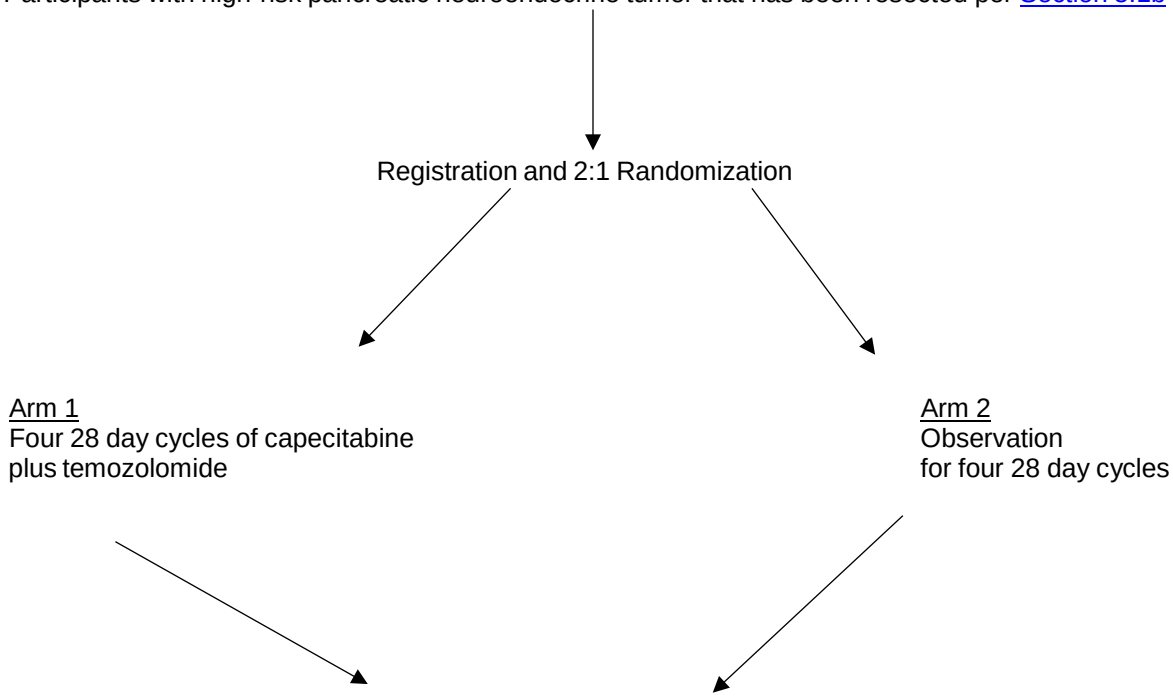
SCHEMA


Participants with high-risk pancreatic neuroendocrine tumor that has been resected per Section 5.1b
Registration and 2:1 Randomization
Arm 1
Four 28 day cycles of capecitabine
plus temozolomide
Arm 2
Observation
for four 28 day cycles
Off treatment follow-up for 5 years from randomization

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a participant to be considered eligible for registration in OPEN. Section 5 may be printed and used by the site but is not to be uploaded in RAVE (unless specifically stated). For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG SDMC in Seattle at 206/652-2267 or giquestion@crab.org prior to registration. **NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).**

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 4 weeks later would be considered Day 28. This allows for efficient participant scheduling without exceeding the guidelines. **If Day 14, 28 or 90 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease-Related Criteria

a. Participants must have a histologic diagnosis of well-differentiated (as defined in Section 4.1) pancreatic neuroendocrine tumor (pNET) that was resected between 14 and 90 days prior to registration. Participants must have a scan within 90 days prior to registration without evidence of metastatic disease. Acceptable scans are multiphase CT abdomen, MRI with IV contrast of the abdomen, or PET-CT DOTATATE imaging if the DOTATATE PET-CT included IV iodine contrast for the CT portion of the exam.

.

b. Resection must have been an R0 or R1 per treating investigator's assessment and/or pathology report. See Section 18.3 for definitions of R0 and R1.

c. Ki-67 testing, which is considered part of standard of care in the pathology report, must have been performed between 14 and 90 days prior to registration and the result must be ≥ 3% and ≤ 55%. Treating investigators are encouraged to contact the **S2104** Study Chairs and/or the study pathology chair with questions. If more than one Ki-67 is reported (e.g., primary tumor versus lymph node or metastatic site), the highest one should be considered for the study eligibility criteria.

d. Participants with localized resected pNETS must have a Zaidi score of ≥ 3 derived by the following factors and points:

Factor	Points
symptomatic tumor defined as one of the following: • Gastrointestinal bleed • Jaundice • Gastrointestinal obstruction • Pain from primary tumor prior to surgical resection • Pancreatitis	1
Primary pancreas tumor size >2 cm	2
Ki-67 3% to 20%	1
Lymph node positivity = 1	1
Ki-67 21% to 55%	6
Total points (score)	

e. Participants may have received resection/ablation of liver oligo-metastatic disease (up to 5 liver metastases) at the time of well-differentiated pNET resection.

f. Participants must not have unresected or unablated metastatic disease.

g. Participants must not have clinically apparent central nervous system metastases or carcinomatous meningitis.

5.2 Prior/Concurrent Therapy Criteria

a. Participants must have recovered from effects of surgery as determined by the treating investigator.

b. Participants must not have received prior neoadjuvant therapy for treatment of pancreatic neuroendocrine tumor. Use of somatostatin analogs prior to surgery is permitted.

c. Participants must not have received somatostatin analogs after surgery.

5.3 Clinical/Laboratory Criteria

a. Participants must be ≥ 18 years old.

b. Participants must have Zubrod Performance Status of 0-2 (see Section 10.1).

c. Participants must have a complete medical history and physical exam within 28 days prior to registration.

d. Participants must have adequate organ and marrow function as defined below within 28 days prior to registration:

- leukocytes ≥ 3 x 10^3/uL
- absolute neutrophil count ≥ 1.5 x 10^3/uL
- platelets ≥ 100 x 10^3/uL
- total bilirubin ≤ institutional upper limit of normal (ULN) unless history of Gilbert's disease. Participants with history of Gilbert's disease must have total bilirubin ≤ 5 x institutional ULN.
- AST and ALT ≤3 × institutional ULN
- serum creatinine ≤ 1.5 x institutional ULN
- calculated creatinine clearance ≥ 50 ml/min

$$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{weight in kg})\ \dagger}{72 \times \text{serum creatinine}\ *}$$

Multiply this number by 0.85 if the participant is female.

† The kilogram weight is the participant weight with an upper limit of 140% of the IBW.
* Actual lab serum creatinine value with a minimum of 0.8 mg/dL.

e. Participants must be able to swallow pills.

f. Participants must be able to tolerate CT or MR imaging including contrast agents as required for their treatment and the protocol.

g. Participants must not be planning to receive warfarin while on protocol treatment. Other anticoagulants are allowed.

h. Participants must not have history of allergic reactions attributed to compounds of similar chemical or biologic composition to temozolomide or capecitabine.

i. Participants must not have known absorption issues that would limit the ability to absorb study agents.

j. Participants must not have had an arterial thromboembolic event, unstable angina, or myocardial infarction within 12 months prior to registration.

k. Participants must not have active or uncontrolled infection.

l. Participants must not have serious medical or psychiatric illness that could affect study participation in the judgement of the treating investigator.

m. Participants must not be pregnant due to the possibility of harm to the fetus. Individuals who are of reproductive potential must have agreed to use an effective contraceptive method with details provided as a part of the consent process. A person who has had menses at any time in the preceding 12 consecutive months or who has semen likely to contain sperm is considered to be of "reproductive potential."In addition to routine contraceptive methods, "effective contraception" also includes refraining from sexual activity that might result in pregnancy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) including hysterectomy, bilateral oophorectomy, bilateral tubal ligation/occlusion, and vasectomy with testing showing no sperm in the semen.

n. No other active malignancy or history of prior malignancy is allowed, except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the participant is currently in complete remission, or any other cancer from which the participant has been disease free for two years.

5.4 Regulatory Criteria

a. Participants ***must*** be informed of the investigational nature of this study and must sign and give informed consent in accordance with institutional and federal guidelines.