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E2211

A Randomized Phase II Study of Temozolomide or Temozolomide and Capecitabine in Patients with Advanced Pancreatic Neuroendocrine Tumors

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Rev. 6/14 ***STUDY PARTICIPANTS***

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

ACTIVATION DATE

April 11, 2013
Addendum #1 - Incorporated Prior to Activation
Update #1 - Incorporated Prior to Activation
Addendum #2 – 2/14
Addendum #3 – 6/14
Update #2 – 5/15
Addendum #4 – 7/15

Agents	IND#	NSC#	Supply
Temozolomide	N/A	NSC 362856	Commercially Available
Capecitabine	N/A	NSC 712807	Commercially Available

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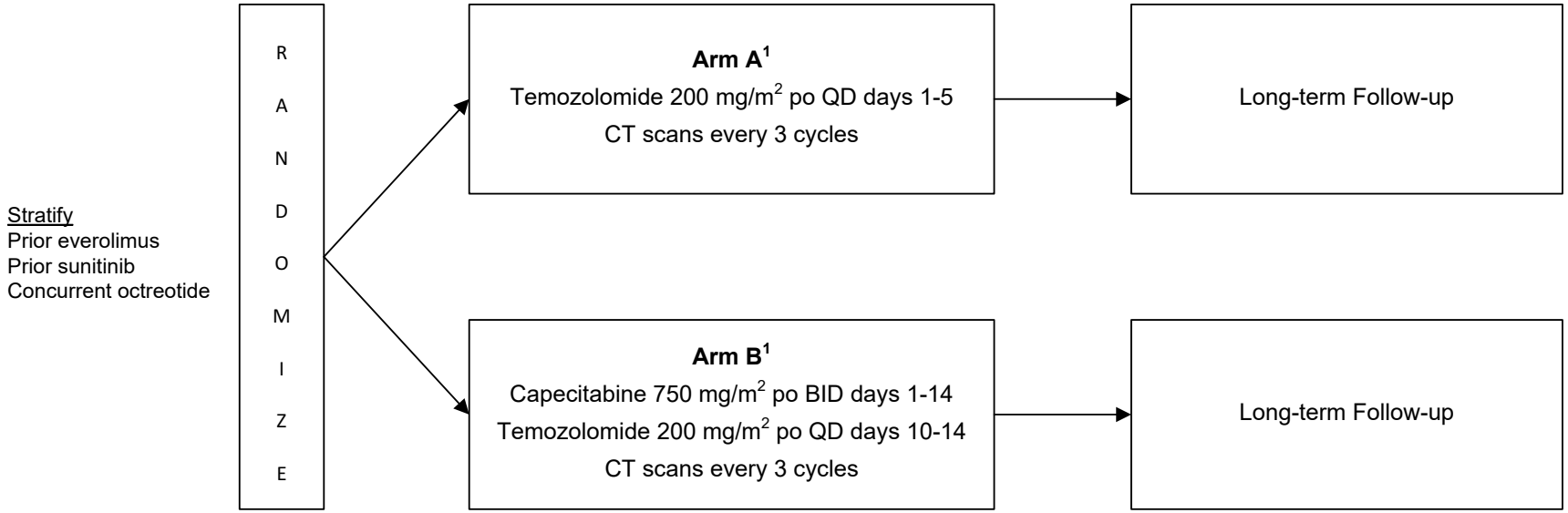
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com...	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most recent version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e. patient eligibility or treatment-related questions) contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical 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 > education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy		
The CTSU Web site is located at https://www.ctsu.org		

Schema



Accrual = 145

Cycle = 28 days

All doses are based on actual body weight.

1. Treatment will continue for up to 13 cycles (approximately 1 year).

1. Introduction

1.1 Rationale for selected approach and trial design

Patients with advanced pancreatic neuroendocrine tumors (NETs) currently have few treatment options that yield objective radiographic tumor regression. Recent studies evaluating everolimus[1] and sunitinib[2] in this patient population have demonstrated prolongation of progression-free survival (PFS) compared to placebo, but overall tumor response rates (by RECIST) with these agents are less than 10%.

Historical studies reporting the highest response rates (RRs) and longest PFS intervals include regimens with cytotoxic chemotherapy. In an initial randomized study of 106 patients, Moertel *et al.* reported activity associated with the combination of streptozocin and doxorubicin in patients with advanced islet-cell tumors.[3] The RR associated with this regimen was reported to be 69% and PFS was 20 months. However, because of the use of non-standard response criteria, the true objective radiologic response rate was likely much lower. Retrospective series have reported overall response rates of 6-39% and PFS of 4-18 months associated with streptozocin-based regimens in pancreatic NETs.[4-6] While clearly associated with activity, the combination of streptozocin and doxorubicin is also associated with considerable toxicity, including myelosuppression, asthenia, and renal insufficiency, precluding its routine use in this disease.

Recent retrospective series and small, prospective phase II studies, described below, suggest that temozolomide is similarly active but less toxic than streptozocin-based therapy in patients with pancreatic NETS. Furthermore, like streptozocin, temozolomide is an alkylating agent that induces methylation at the O6 position of guanine, suggesting that expression of the DNA repair enzyme methyl guanine methyltransferase (MGMT) may correlate with treatment response to temozolomide. Based on these studies, temozolomide-based therapy is listed on NCCN guidelines and is included in the Medicare compendium for use in pancreatic NETs. There is, nevertheless, little consensus on the optimal temozolomide regimen to use in patients with pancreatic NETs, nor has temozolomide been evaluated prospectively in a multi-institutional setting in patients with advanced pancreatic neuroendocrine tumors.

The proposed study will provide prospective data on response rates and progression-free survival associated with temozolomide or temozolomide in combination with capecitabine, and will also assess the relative efficacy of these two regimens. The study further explores whether, as has been shown in glioblastoma, MGMT deficiency as determined by promoter methylation and immunohistochemistry, predicts response in patients with pancreatic NETs treated with these regimens.

We propose a multi-institutional randomized study of temozolomide administered with or without capecitabine in advanced pancreatic neuroendocrine tumor patients (using dosing as per the Strosberg regimen[16]). The principal objective of the study will be to evaluate PFS associated with temozolomide alone or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors. Secondary objectives will be to assess the tumor response rates, overall survival, and toxicity associated with these regimens. A

correlative study will assess whether MGMT deficiency is associated with temozolomide response.

1.2 Clinical relevance of study

Streptozocin-based therapy was associated with a survival benefit in one randomized study of pancreatic NETs[3] and is currently the only FDA-approved cytotoxic agent for use in this disease. However, because of its potential for toxicity and production shortage, its use in pancreatic NETs is not widespread. Both retrospective and small, prospective studies suggest that temozolomide-based regimens are an active and potentially less toxic oral alternative to streptozocin-based therapy in pancreatic NETs. Based on these studies, temozolomide is increasingly used for this indication and is included in both NCCN guidelines and the Medicare compendium.

There have been no prospective studies evaluating the antitumor activity of temozolomide alone in patients with neuroendocrine tumors. Similarly, the current common use of a temozolomide/capecitabine combination regimen is based on data from a 30-patient, retrospective, single-institution series; the temozolomide/capecitabine regimen has not been formally evaluated in a prospective phase II study. A need to formally evaluate the activity of temozolomide in pancreatic neuroendocrine tumors, and to compare single agent vs. combination therapy in this disease was highlighted in the NCI Neuroendocrine Tumor Clinical Trials Planning Meeting (CTPM).

The currently proposed study responds to this recommendation. We note that temozolomide alone is considered the reference arm for this study, despite the absence of prospective data for this combination in neuroendocrine tumors. We considered several alternative options in making this decision. Ideally, a placebo arm would be used as a reference, as was done in the RADIANT 3 and sunitinib randomized studies. However, a placebo was not considered appropriate or feasible in light of the fact that temozolomide is included in treatment compendia based on retrospective and small prospective series demonstrating antitumor activity. A streptozocin control arm was not considered feasible based on toxicity concerns, as well as, concerns regarding drug supply. A control arm of everolimus or sunitinib was considered; however, there was little enthusiasm for directly comparing a cytotoxic chemotherapy regimen to a targeted agent. Indeed, a current treatment paradigm is starting with targeted therapy in most patients, and using a cytotoxic regimen as a salvage therapy. A goal of this study is to establish clear prospective data for two promising cytotoxic regimes and to gain a preliminary assessment of their relative activity.

Additionally, preliminary data described in the correlative section of this proposal suggest that the anti-tumor activity of temozolomide is associated with the DNA repair enzyme MGMT. The identification of biomarkers predictive of tumor response was an additional recommendation of the Neuroendocrine Tumor CTPM. Data derived from studies in glioblastoma strongly suggest a correlation between MGMT silencing and response to temozolomide-based therapy, as does retrospective data in pancreatic neuroendocrine tumors. The correlative component of this study will assess whether MGMT promoter methylation status is associated with the activity of temozolomide-based therapy. A positive association could provide justification for the use of MGMT expression as a

determinant for which pancreatic neuroendocrine tumor patients should receive temozolomide-based treatment.

1.3 All relevant data that justify the use of the control and experimental arms

Antitumor activity associated with temozolomide in neuroendocrine tumors has been reported in a number of retrospective series. In a retrospective series of 36 patients treated with temozolomide monotherapy, tumor regression was observed in 31% of bronchial carcinoid tumors and 8% of pancreatic neuroendocrine tumors; median time to progression (TTP) was 7 months for all patients.[7] In a series of 97 patients, 18 of 53 patients with pancreatic NETs (34%) achieved a partial or complete response to temozolomide-based therapies; median PFS was 13.6 months for those patients.[8] A third retrospective series of 21 patients treated with temozolomide monotherapy demonstrated responses in 25% of pancreatic NETs, median PFS was 9.1 months.[9]

Temozolomide has additionally been investigated prospectively in small phase II studies of patients with neuroendocrine tumors, though always in combination with other agents. In an initial study, 29 patients with metastatic neuroendocrine tumors were treated with a combination of temozolomide, administered at a dose of 150 mg/m^2 for 7 days, every other week, and thalidomide at doses of 50 to 400 mg daily; this combination was associated with objective tumor responses in 5/11 patients. Median PFS was not reached.[10] A subsequent phase II study evaluated the combination of temozolomide and bevacizumab in 34 patients with neuroendocrine tumors (15 pancreatic, 19 carcinoid).[11] Patients received temozolomide, 150 mg/m^2/day po for 7 days every other week, and bevacizumab, 5 mg/kg IV every other week. Due to anticipated lymphopenia, patients also received prophylaxis with trimethoprim/sulfamethoxazole (1 DS tablet q MWF). Objective tumor responses were observed in 33% of patients with pancreatic neuroendocrine tumors with median PFS of 14.3 months for these patients (M Kulke, personal communication). In a third prospective study a regimen of temozolomide and everolimus was associated with an overall tumor response rate of 35% in patients with advanced pancreatic NET, median PFS was not reported.[12]

Interestingly, pre-clinical and early clinical evidence suggest that capecitabine may be synergistic with temozolomide.[13,14] In a series of 17 patients with pancreatic NETs, combination therapy with temozolomide and capecitabine was associated with a tumor response rate of 59%, median PFS was not reported.[15] A recent single-institution retrospective study by Strosberg *et al.* reported response rates of 70% and a median PFS of 18 months in 30 patients with advanced pancreatic NETs[16]. In this study, temozolomide was administered at a dose of 200 mg/m^2 days 10-14, and capecitabine was administered at a dose of 750 mg/m^2 BID d1-14. The combination and specific dosing schedules reported were very well tolerated with only 4 patients experiencing grade 3 or 4 adverse events (anemia, thrombocytopenia, elevated AST and elevated ALT). The most common grade 1 and 2 adverse events were fatigue, nausea, myelosuppression and hand-foot syndrome. Based on this study, the combination of temozolomide and capecitabine has become popular and commonly used in patients with advanced pancreatic neuroendocrine tumors.

Taken together, these prospective and retrospective studies suggest that temozolomide-based therapy is comparable to streptozocin-based regimens and might reasonably be expected to be associated with an overall median PFS of 7-14 months in patients with advanced pancreatic NET. To date, no prospective studies have evaluated the antitumor activity of temozolomide alone in pancreatic neuroendocrine tumors, nor have any prospective studies formally evaluated the combination of temozolomide and capecitabine in this setting. As noted above, despite the absence of prospective data, temozolomide alone is considered a reference arm in this study based on the strength of prior retrospective and limited prospective data demonstrating activity with temozolomide containing regimens in this setting, and the inclusion of temozolomide in treatment compendia. Strong historical control data from the placebo arms of the randomized studies of everolimus (showing a PFS of 5.5 months)[1] and sunitinib (showing a PFS of 4.5 months)[2] should provide a reasonable basis for assessment of the antitumor activity associated with temozolomide alone. Additionally, these two regimens have never been formally compared.

The proposed study will compare the temozolomide/capecitabine combination (as reported by Strosberg and colleagues), in which temozolomide is administered during a 28 day cycle at a dose of 200 mg/m^2 days 10-14 of 28 day cycles and capecitabine is administered at a dose of 750 mg/m^2 BID days 1-14 of 28 day cycles, to single agent temozolomide. We note that prior prospective studies of temozolomide have used a dose-intense regimen of 150 mg/m^2 for 7 days, administered every other week, but that this regimen has been associated with significant lymphopenia and need for prophylaxis. To reduce this risk, and to facilitate comparison with the combination regimen, we have elected to use a single-agent temozolomide regimen of 200 mg/ m^2 days 1-5 of a 28-day regimen in our study. We further plan to limit the total duration of treatment to 13 cycles (approximately 1 year).

1.4 Rationale for Laboratory Research Studies

1.4.1 Evaluation of MGMT status by Immunohistochemistry (IHC)

Temozolomide is an alkylating agent initially developed as an oral and more easily tolerated alternative to dacarbazine. The cytotoxic effect of temozolomide has been attributed to its ability to induce DNA methylation at the O6 position of guanine. Methylation of guanine results in DNA mismatch, ultimately resulting in apoptosis and tumor cell death.[17] The sensitivity of tumor cells to alkylating agents, including temozolomide, has been associated with decreased levels of the DNA repair enzyme, O6-methylguanine DNA methyltransferase (MGMT), which, through its ability to restore DNA to its normal form, can prevent chemotherapy-induced cell death.[18] Decreased levels of MGMT have been associated with clinical benefit and enhanced survival in melanoma and glioblastoma patients treated with temozolomide.[19-23]

In a study by Kulke, et al., 97 archival neuroendocrine tumors specimens were evaluated for MGMT deficiency by immunohistochemistry.[8] Among 37 pancreatic neuroendocrine tumors evaluated, 19 (51%) were MGMT deficient. Non-functional tumors included similar proportions of MGMT intact and MGMT deficient

tumors. Three of 10 insulinomas were MGMT deficient; both gastrinomas and the single evaluated glucagonoma were also MGMT deficient. In contrast, MGMT was present in all 60 carcinoid tumors (20 typical bronchial carcinoids, 20 atypical bronchial carcinoids and 20 small intestine carcinoids) evaluated. Among 21 patients with evaluable tumor tissue who had also received treatment with temozolomide, 4 of 5 patients with MGMT-deficient tumors (all pancreatic NETs) and 0 of 16 patients with MGMT-intact tumors responded to treatment (p=0.001).

1.4.2 Evaluation of MGMT status by Promoter Methylation

The clinical utility of assessing MGMT promoter methylation status was first demonstrated in patients with gliomas. Gliomas are the most common primary brain tumors. Grade IV gliomas, also known as glioblastoma multiforme (GBM) are highly malignant tumors that account for almost a third of primary brain tumors in adults. Patients with gliomas that exhibited promoter methylation of the MGMT gene showed modestly longer survival after treatment with alkylating chemotherapeutics than patients whose gliomas did not show MGMT promoter methylation. Clinical trials to evaluate the use of MGMT promoter methylation to predict response to alkylating agents have also been designed for patients with acute myeloid leukemia, neuroendocrine tumors, and other cancers.

The mechanisms of MGMT regulation in neuroendocrine tumors remain unknown. Silencing of the MGMT gene by CpG island promoter methylation is a common mechanism of MGMT regulation in other tumor types. In patients with glioblastoma, MGMT promoter methylation is associated with improved survival and benefit from temozolomide.[22,24] Limited studies of CpG island methylation in neuroendocrine tumors however, have found either no significant difference in MGMT promoter methylation rates between carcinoid and pancreatic neuroendocrine tumors, or higher rates of promoter methylation in carcinoid tumors compared to pancreatic neuroendocrine tumors.[25,26]

Further studies to evaluate whether promoter methylation is a common MGMT silencing mechanism in neuroendocrine tumors, and whether promoter methylation correlates with immunohistochemical absence of MGMT, are warranted.

2. Objectives

2.1 Primary Endpoints

2.1.1 To evaluate PFS associated with temozolomide alone or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors.

2.2 Secondary Endpoints

2.2.1 To evaluate response rates (RR) associated with temozolomide alone or temozolomide and capecitabine treatment in patients with advanced pancreatic neuroendocrine tumors.

2.2.2 To evaluate overall survival (OS) associated with temozolomide alone or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors.

2.2.3 To evaluate the toxicity associated with temozolomide alone or temozolomide and capecitabine treatment in patients with advanced pancreatic neuroendocrine tumors.

2.2.4 To evaluate the usefulness of MGMT status (by IHC and promoter methylation) for predicting response in pancreatic neuroendocrine tumor patients treated with either temozolomide or temozolomide and capecitabine.

2.2.5 To bank radiology images for evaluation of quality, reproducibility, and compliance with CT methodology.

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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) _____

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.

3.1 Eligibility Criteria

_____ 3.1.1 Patient must have histologically or pathologically confirmed locally unresectable or metastatic low or intermediate grade pancreatic neuroendocrine tumor, excluding small cell carcinoma.

_____ 3.1.2 Patient must have measurable disease by RECIST 1.1 criteria as defined in Section 6.1.2. Baseline measurements and evaluations of all sites of disease must be obtained ≤ 4 weeks prior to randomization and must be acquired by multiphasic CT or contrast MRI.

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_____ 3.1.3 Patient must have documented disease progression, and date of last documented disease progression must be within 12 months from date of randomization.

_____ 3.1.4 Patient must not have received prior temozolomide, DTIC, capecitabine, or 5-FU therapy.

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_____ 3.1.5 Prior everolimus and/or sunitinib therapy is allowed, so long as it was discontinued ≥ 4 weeks prior to randomization.

_____ 3.1.6 Concurrent somatostatin analogues are allowed provided that the patient 1) has been on a stable dose (+/- 10mg) for 8 weeks and 2) has documented disease progression on that dose.

_____3.1.7 Chemoembolization is allowed if ≥ 4 weeks from study entry. There are 3 possible scenarios:

_____ 3.1.7.1 If patient has hepatic disease only: they need to have progressed in the liver since chemoembolization and have measureable disease by RECIST 1.1 in order to be eligible.

_____ 3.1.7.2 If patient has hepatic and extrahepatic disease: they will need to have progressed inside OR outside the liver and

have measureable disease by RECIST 1.1 in order to be eligible.

_____ 3.1.8 Patients may not be receiving any other investigational agents while on study treatment.

_____ 3.1.9 Patients may not be receiving Coumadin while on treatment. Other anticoagulants are allowed.

_____ 3.1.10 Patients must have normal organ and marrow function as defined below within ≤ 14 days prior to randomization:

_____ 3.1.10.1 Leukocytes ≥ 3,000/mm^3

Leukocytes_____ Date:_____

_____ 3.1.10.2 Absolute neutrophil count ≥ 1,500/mm^3

Neutrophil count:_____ Date:_____

_____ 3.1.10.3 Hemoglobin ≥ 9 g/dL

Hemoglobin:_____ Date:_____

_____ 3.1.10.4 Platelets ≥ 100,000/mm^3

Platelets: _____ Date:_____

_____ 3.1.10.5 Total bilirubin ≤ institutional upper limit of normal (ULN) or ≤ 1.5 X institutional ULN (if the patient has liver metastases).

ULN: _____ Bilirubin:_____ Date:_____

_____ 3.1.10.6 AST(SGOT)/ALT(SGPT) ≤ 3 X institutional ULN or (≤ 5 X institutional ULN if the patient has liver metastases).

ULN: _____ AST_____ Date:_____

ULN: _____ ALT_____ Date:_____

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_____ 3.1.10.7 Serum Creatinine ≤ 1.5 X institutional ULN

ULN: _____ Creatinine:_____ Date:_____

_____ 3.1.11 Patient must be at least 18 years of age.

_____ 3.1.12 Patient must have ECOG performance status 0-1.

_____ 3.1.13 Patient must have life expectancy ≥ 12 weeks.

_____ 3.1.14 Patients with either clinically apparent central nervous system metastases or carcinomatous meningitis are ineligible.

_____ 3.1.15 Patients must NOT have active or uncontrolled infection or serious medical or psychiatric illness.

_____ 3.1.16 Patients must NOT have history of allergic reactions attributed to compounds of similar chemical or biologic composition to temozolomide or capecitabine.

_____ 3.1.17 Patient must NOT have absorption issues that would limit the ability to absorb study agents.

_____ 3.1.18 Patients with a history of the following within ≤ 12 months of study entry are not eligible.

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

_____ 3.1.19 Patients with symptomatic peripheral vascular disease are not eligible.

_____ 3.1.20 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, or breast cancer in situ.

OR

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

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OR

- Prior malignancy cured by non-surgical modalities and patient has been continuously disease free for > 5 years.

Date of last evidence disease:_____

_____ 3.1.21 Women must not be pregnant or breast-feeding due to potential harm to fetus from temozolomide and/or capecitabine.

All females of childbearing potential must have a blood test or urine study within ≤ 2 weeks prior to randomization to rule out pregnancy. A female of childbearing potential is any woman, 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 of childbearing potential? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.1.22 Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception or to abstain from sexual intercourse for the duration of their participation in the study. 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.

_____ 3.1.23 Patient must be able to swallow pills.

_____ 3.1.24 Patient must be able to tolerate CT or MR imaging including contrast agents as required for their treatment and the protocol.

_____ _____

Physician Signature Date

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

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4. Randomization Procedures

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU Registration Procedures

Rev. 7/15

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

IRB Approval:

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 be approved to 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. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the E2211 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the **ECOG-ACRIN** link to expand, then select trial protocol **E2211**
- Click on the Site Registration Documents link

Requirements for E2211 site registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents

Submit completed forms along with a copy of your IRB Approval *and Model Informed Consent* to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
FAX: (215) 569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

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**

Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Patient Enrollment

Patients must not start protocol treatment prior to randomization.

Rev. 6/14, 7/15 **Treatment should start within ten working days after randomization.**

Patient randomization 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.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://eapps-ctep.nci.nih.gov/iam/index.jsp>) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. 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.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

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.

The following information will be requested:

4.1 Protocol Number

4.2 Investigator Identification

4.2.1 Institution and affiliate name (Institution CTEP ID)

4.2.2 Investigator's name (NCI number)

4.2.3 Cooperative Group Credit

4.2.4 Credit Investigator

4.2.5 Protocol specific contact information

4.3 Patient Identification

4.3.1 Patient's initials (first and last)

4.3.2 Patient's Hospital ID and/or Social Security number

4.3.3 Patient demographics

4.3.3.1 Gender

4.3.3.2 Birth date

4.3.3.3 Race

4.3.3.4 Ethnicity

4.3.3.5 Nine-digit ZIP code

4.3.3.6 Method of payment

4.3.3.7 Country of residence

4.4 Eligibility Verification

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

4.5 Stratification Factors

Patients will be stratified according to the following factors for purposes of balancing arms:

4.5.1 Prior everolimus: Yes v. No

4.5.2 Prior sunitinib: Yes v. No

4.5.3 Concurrent octreotide: Yes v. No

4.6 Additional Requirements

4.6.1 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.

4.6.2 The IRB-approved consent must allow patients the option to provide specimens to for use in undefined future research.

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4.6.3 Biological samples to be submitted as indicated in Section 11.

4.6.4 Imaging studies are to be submitted as outlined in Section 10.

4.6.5 Data collection for this study will be done exclusively in Medidata Rave. Study staff will receive an invitation to join the study in Rave

after evidence of IRB approval is submitted to RSS. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS after IRB approval is obtained. 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-mails 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 www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

4.7 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 according to the instructions in the E2211 Forms Completion Guidelines.

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5. Treatment Plan

5.1 Administration Schedule

One cycle = 28 days

All doses are based on actual weight. If there is a < 5% change in Body Surface Area (BSA), keep the doses the same. If there is a ≥ 5% change in BSA, a new dosing weight and BSA should be set and used for dose calculations.

- Temozolomide
  - The temozolomide dose will be capped at 400 mg daily. The calculated dose by BSA will be rounded down to minimize the number of capsules required. The treating investigator should use their best judgment to meet these guidelines.
  - Temozolomide sould be taken by mouth at night after fasting from solid food for two hours. Temozolomide capsules must not be crushed and must be administered whole.
  - Temozolomide missed doses will not be made up and patients should not double-up on missed doses during treatment.
  - Ondansetron or other anti-emetic is strongly suggested as a premedication 30-60 minutes prior to temozolomide. Otherwise, anti-emetics, anxiolytics, and analgesics may be provided at physicians' discretion.
- Capecitabine
  - The calculated total daily capecitabine dose by BSA will be rounded down to allow doses using 500 mg tablets. Investigators should approximate the calculated dose based on the pill size available while rounding down to minimize the number of capsules required. The treating investigator should use their best judgment to meet these guidelines.
  - Capecitabine should be taken morning and night, with at least 8 hours between each dose. Capecitabine tablets should be swallowed with water within 30 minutes after a meal.
  - Capecitabine missed doses will not be made up and patients should no double-up on missed doses during treatment.

NOTE: Monitor CBC and platelet count prior to drug administration.

5.1.1 ARM A

Temozolomide 200 mg/m^2 po QD days 1-5

Repeat cycles every 28 days

Maximum duration of treatment 13 cycles (approximately 1 year)

5.1.2 ARM B

Capecitabine 750 mg/m^2 po BID days 1-14

Temozolomide 200 mg/m^2 po QD days 10-14

Repeat cycles every 28 days

Maximum duration of treatment 13 cycles (approximately 1 year)

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5.2 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 the 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.
- **Expectedness:** Any adverse event, the type or severity of which is consistent with the current investigator's brochure, product label, and/or the protocol document

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)
- the FDA (800-332-1088)

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

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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. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178) in the same timeframe.

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.

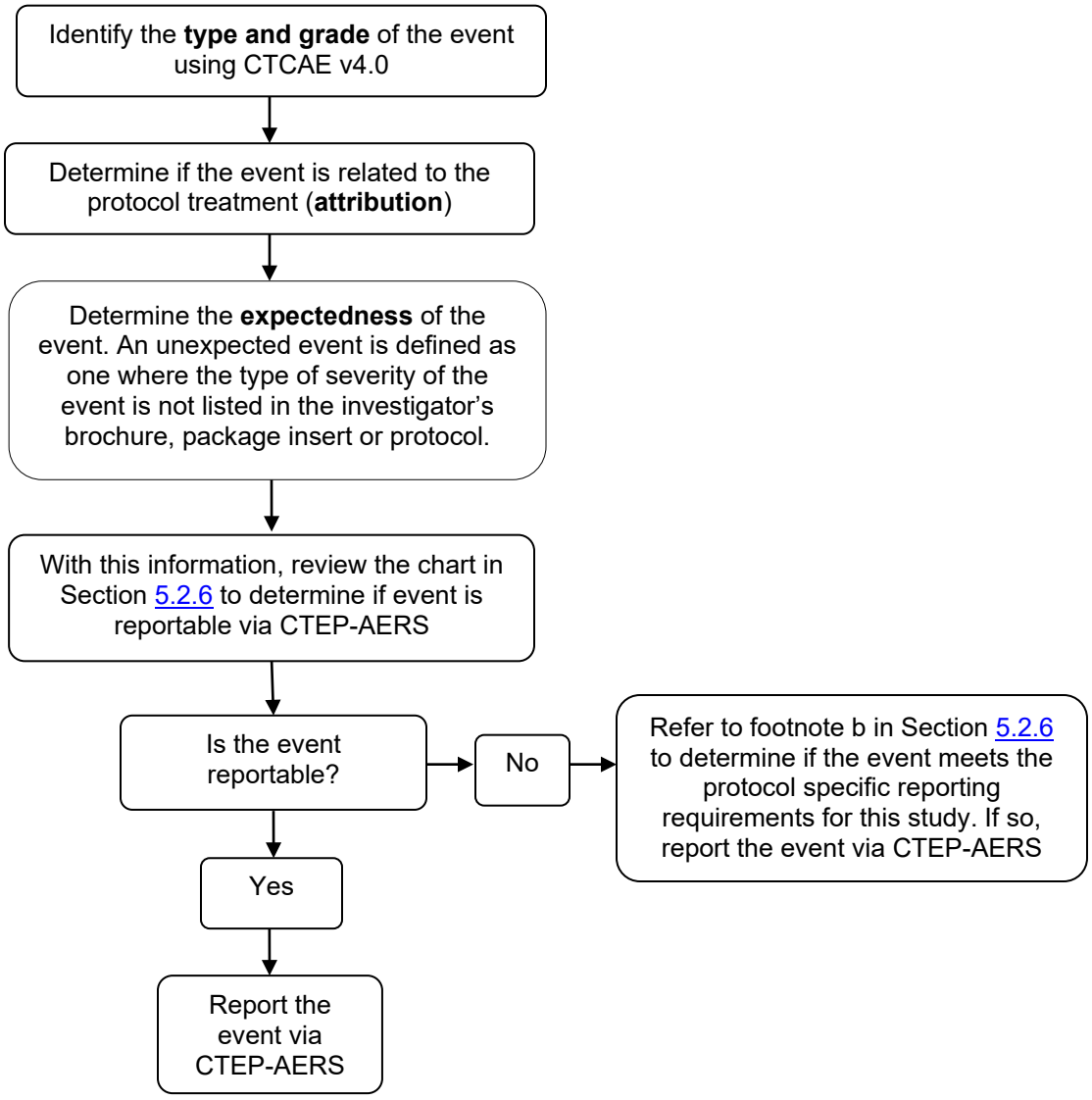
5.2.4 Determination of reporting requirements

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 Common Terminology Criteria for Adverse Events (CTCAE) grade
- the relationship to the study treatment (attribution)
- the expectedness of the adverse event

Using these factors, the instructions and tables in the following sections have been customized for protocol E2211 and outline the specific expedited adverse event reporting requirements for study E2211.

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



5.2.6 Expedited Reporting Requirements for Arms A and B on protocol E2211

Commercial Agents: Temozolomide and Capecitabine

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only – (Arms A and B)

Attribution	**Grade 4**		**Grade 5[a]**		**ECOG-ACRIN and Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	See footnote (b) for special requirements.
Unrelated or Unlikely			7 calendar days	7 calendar days	
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a This includes all deaths within 30 days of the last dose of treatment regardless of attribution. **NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event**.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these 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.

5.2.7 Other recipients of adverse event reports and supplemental data

ECOG-ACRIN will forward CTEP-AERS reports to the appropriate regulatory agencies and pharmaceutical company, if applicable.

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.

5.2.8 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:**

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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 <u>secondary malignancy</u> 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:**

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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 <u>not</u> 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

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5.3 <u>Dose Modifications</u>

5.3.1 General

Initial doses of capecitabine will be based on BSA (i.e. 750 mg /m^2 po BID). Initial doses of temozolomide will be based on BSA, unless over the 400 mg cap in which case 400 mg will be used as the total daily dose.

If BSA-based dose is used for a patient, dose reductions for weight change or toxicity will be based on the total daily dose (see Capecitabine and Temozolomide Dose Table).

If temozolomide cap is used, dose reductions for weight change will only be made if recalculated dose is less than 400 mg. If temozolomide cap is used, dose reductions for toxicity will be based on the total daily dose.

If dose reduction is required, reduction is permanent. Missed doses will not be made up.

Dose will be modified for all drugs if there is a ≥ 5% change in patient's BSA while on study.

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.

For Arm B, patients may discontinue one agent due to toxicity and continue the other on-study.

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

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*****NOTE: If patient has been off treatment for any reason > 4 weeks from next planned cycle start date, patient must discontinue protocol treatment.**

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) 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 Temozolomide Dose Modifications

The dose of temozolomide will be determined according to (1) non-hematologic AEs during the previous cycle, as well as (2) the lowest ANC and platelet counts during that cycle.

- Dose reductions: For non-hematologic grade 3 AEs (except for nausea and vomiting as well as AEs unrelated to treatment) the dose should be reduced according to the Temozolomide Hematologic and Other Toxicities charts below. Dose reductions for treatment day ANC and platelet counts should also be made according to the Hematologic chart below. No dose escalation of temozolomide is permitted
- Discontinuation: For patients who require more than 2 dose reductions, temozolomide will be permanently discontinued. For any non-hematologic drug-related grade 4 AEs that does not resolve within the allowed 4 weeks, then temozolomide treatment will be permanently discontinued. Also, except for nausea and vomiting, if any of the same non-hematologic grade 3 AEs that are at least possibly related to study treatment recur after reduction for that AE, then temozolomide will be stopped.

Hematologic Toxicity

ANC (/mm^3)		Platelets (/mm^3)	% of Planned Temozolomide
≥ 1500/mm^3	and	≥ 100,000/mm^3	100%
500-1499/mm^3	or	40,000-99,999/mm^3	Hold* until ANC ≥ 1500/mm^3 and PLT ≥ 100,000/mm^3; resume at 20% dose reduction.
< 500/mm^3	or	< 40,000/mm^3	Hold** until ANC ≥ 1500/mm^3 and PLT ≥ 100,000/mm^3; resume at 40% dose reduction.

* Two total dose reductions are permitted before temozolomide will be discontinued.

** One dose reduction is permitted before temozolomide will be discontinued.

Other Toxicity

For other hematologic toxicities not included in the table above and non-hematologic toxicities, dose reductions of temozolomide will be at the discretion of the investigator. A maximum of 2 dose reductions can be performed in increments of 20% or a single dose reduction of 40%. For patients with significant liver function abnormalities the benefits and risks of continuing treatment should be carefully considered.

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5.3.3 Capecitabine Dose Modifications

Capecitabine will be initiated at 750 mg/m^2 PO BID x 14 days on a 28-day cycle.

Two total dose reductions are permitted before capecitabine will be discontinued. Each dose reduction will be a 20% reduction from the prior level.

Hematologic Toxicities

ANC (/mm^3)		Platelets (/mm^3)	Modification
< 1500/mm^3	AND/OR	< 100,000/mm^3	Hold until ANC ≥ 1500/mm^3 and PLT ≥ 100,000/mm^3; resume at 20% dose reduction
≥ 1500/mm^3	AND	≥ 100,000/mm^3	No dose modification

Mucositis, Diarrhea or Esophagitis

Grade	Toxicities/Symptoms	Modification
1	Mucositis, esophagitis, or diarrhea	No dose modification
2	Diarrhea	No dose modification
2	Mucositis, or esophagitis	Hold until ≤ grade 1 and resume at 20% dose reduction
3	Diarrhea	Hold until ≤ grade 1; resume at 20% dose reduction
3/4	Mucositis or esophagitis	Hold until ≤ grade 1; resume at 20% dose reduction

Palmar – Plantar Erythrodysesia Syndrome (Hand and Foot Rash)

Grade	Modification
1	No dose modification
2	Hold until symptoms resolve to grade 0 or 1. Resume at 20% dose reduction.
≥ 3	Hold until symptoms resolve to grade 0 or 1. Resume at 20% dose reduction.

Other Toxicity

For other hematologic toxicities not included in the tables above and non-hematologic toxicities, dose reductions of capecitabine will be at the discretion of the investigator. A maximum of 2 dose reductions can be performed in increments of 20%.

5.4 Supportive Care

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

5.4.2 Ondansetron is required as a premedication 30 minutes prior to temozolomide. Otherwise, anti-emetics, anxiolytics, and analgesics may be provided at physicians' discretion.

5.5 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 **E2211** 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 progression per protocol criteria or death.

5.5.6 Patient completes 13 cycles of therapy (approximately 1 year of treatment).

5.6 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, 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

6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in RECIST.

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and **never more than four weeks** before randomization.
2. Measurable disease is defined by the presence of at least one measurable lesion.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Evaluable for Objective Response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

(**NOTE:** Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target lesion assessment. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.1.2 Disease Parameters

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm

with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

NOTE: Tumor lesions that are situated in a previously irradiated area are measurable if they demonstrate recent evidence of progression.

Malignant Lymph Nodes

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

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Non-measurable also includes lesions that are < 20 mm by chest x-ray.

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

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

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any

objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

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

6.1.3 Methods for Evaluation of Disease

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

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

Clinical Lesions

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

Conventional CT and MRI

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up must be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior

scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor Markers

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology

These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR)

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

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
(**NOTE:** The appearance of one or more new lesions is also considered progression, See Section 6.1.4.3).

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 8 weeks.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis)

Non-CR/Non-PD

Persistence of one or more non-target lesion(s).

Progressive Disease (PD)

Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions (see Section 6.1.4.3). *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will
therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from "trace" to "large", an increase in nodal disease from "localized" to "widespread", or an increase sufficient to require a change in therapy.

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

6.1.4.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if it:

a) increases in size to ≥ 15 mm in the short axis, or b) there is new pathological confirmation that it is disease (regardless of size).

6.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression or initiation of non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the protocol treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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

Target Lesions	Non-Target Lesions	New Lesions*	Best Overall Response	Remarks
CR	CR	No	CR	≥ 4 wks. Confirmation
CR	Non-CR/Non-PD***	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	
SD	Non-PD***/not evaluated	No	SD	Documented at least once ≥ 8 wks. from study entry
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD***	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.

NOTE: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

6.1.4.5 Duration of Response

Duration of Overall Response

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

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

Duration of Stable Disease

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

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 8 weeks.

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7. Study Parameters

7.1 Therapeutic Parameters

7.1.1 To be completed within 14 DAYS before randomization:

- All blood work, including pregnancy test.

7.1.2 To be completed within 28 DAYS before randomization:

- CT or MRI should be performed.

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	≤ 4 weeks Prior to Randomization	Day 1 of each cycle[4]	Every 3 cycles	End of Treatment[12]	Post Treatment to 5 years from study entry[1]
Tests & Observations					
History and Progress Notes[4]	X	X		X	X
Physical Examination[4]	X	X		X	X
Pulse, Blood Pressure[4]	X	X			
Weight/BSA[4]	X	X			
Performance Status[4]	X	X			
Tumor Measurements[4]	X		X	X	X[7]
Adverse Event Assessment		X		X	X
Laboratory Studies					
CBC, Diff, Platelets[4]	X[6]	X			
Serum Electrolytes and Chemistry[2,4]	X[6]	X		X[12]	
Tumor markers[11,4,13]	X[6]		X		
Pregnancy Test (serum or urine HCG)	X[3]				
CT Scan and/or MRI [4,5,10,13]	X		X	X	X[7]
Specimen Submissions			See Sections 11 and 12		
MANDATORY: Tumor Tissue FFPE[8]	X				
Peripheral blood, ACD or EDTA tube[9]	X				

1. Monitor for survival every 3 months until patient is two years from randomization, then every 6 months until patient is 5 years from randomization. Follow-up is no longer required after patient is more than 5 years from randomization. Once the patient progresses, adverse event assessments no longer need to be performed.

Rev. 6/14 2. Serum electrolytes: Na+, K+, bicarbonate, Cl, BUN, creatinine, glucose; total bilirubin, SGOT(AST), SGPT(ALT), alkaline phosphatase, albumin, total protein, calcium. Serum electrolytes and chemistry must be done within 1 week of start of Cycle 1 and ≤ 72 hours prior to each subsequent treatment cycle.

3. Within 2 weeks of randomization for women of childbearing potential.

4. Labs and physical exam must be done within 1 week of start of Cycle 1. After Cycle 1, Day 1, the start of each treatment cycle may be scheduled up to three days after the expected Day 1 of that cycle. History and Progress Notes; Physical Examination; Pulse, Blood Pressure; Weight/BSA; Performance Status; CBC, Diff, Platelets; Serum Electrolytes and Chemistry, and Adverse Event Assessment must be done ≤ 72 hours prior to each treatment cycle.

5. If only MRI of the abdomen and/or pelvis is available, this can be substituted for CT of abdomen and/or pelvis, but CT of chest should still be obtained. Copies of all standard-of-care imaging studies are to be submitted to the American College of Radiology Imaging Network (ACRIN) and the ACR Imaging Core Lab as outlined in Section 10.

6. Must be done within 2 weeks prior to randomization.

7. Post treatment scans will be performed every 3 months for 3 years from randomization and every 6 months between 3-5 years from randomization. The collection of tumor markers is encouraged at this time, but not required. Once there is confirmation of progression, scans and tumor measurements no longer have to be performed.

Rev. 6/14 8. Representative tumor tissue (block preferred) and related pathology reports are to be submitted for central diagnostic review and classification and defined research studies within 4 weeks following randomization as outlined in Section 11. Failure to submit the required materials may render the case unevaluable but will not impact patient participation in the trial.

9. Research blood sample may be collected at any time during the trial, although prior to start of treatment is preferred. EDTA may be used if ACD not available. Submit from patients who answer “Yes” to “I agree to provide additional blood for research” as outlined in Section 12.

Rev. 6/14 10. Imaging instructions: All standard-of-care imaging studies (including CT, MRI, PET, perfusion CT, or any combination) of the abdomen and pelvis will be submitted to ACRIN via the ACR Imaging Core Lab per Section 10.2 instructions. Submission of chest images is optional. Preferably, a minimum of three (3) image phases will be submitted (see below):

Preferred:

- Late arterial phase through the abdomen
- Portal venous phase through the abdomen and pelvis
- Delayed (equilibrium) phase through the abdomen at 3 to 4 min after contrast administration.

If performed per standard institutional practice:

- Perfusion CT sequences of an area of interest is optional and should be performed according to site specific specifications if available at the participating institution.

11. Tumor markers: Chromogranin A and Neuron Specific Enolase (NSE) are required at baseline and every 3 cycles. Other tumor markers may be done at the investigator’s discretion and based on patient symptoms (i.e. glucagon, insulin, VIP, pancreatic polypeptide, gastrin). Continued collection of tumor markers is encouraged during the follow-up period.

Rev. 2/14, 6/14 12. End of Treatment assessments and labs must be performed within 4 weeks after patient’s last date of protocol treatment. CT scan and/or MRI performed within 30 days of the last date of protocol treatment do not need to be repeated at End of Treatment.

Rev. 6/14 13. After randomization, the CT scan or MRI, Tumor Measurements, and Tumor Markers will be completed every 3 cycles. Should the 3 cycle interval be delayed or extended, the next interval scan and tumor markers should be completed no more than 16 weeks from previous scan (≤ 4 weeks from planned scan date).

8. Drug Formulation and Procurement

Both temozolomide and capecitabine will be obtained commercially.

8.1 Temozolomide

8.1.1 Other Names

Temodar

8.1.2 Classification

Cytotoxic chemotherapy, alkylating agent

8.1.3 Mode of Action

Temozolomide [8-carbamoyl-3-methylimidazo(5,1-d)-1,2,3,5-tetrazin-4(3H)-one] (Temodal) is an imidazole tetrazinone compound developed by Schering-Plough for use as an antineoplastic agent. TMZ is a prodrug that spontaneously hydrolyzes to 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC), which is also the active metabolite of dacarbazine. Dacarbazine, however, requires hepatic metabolism for formation of this metabolite, which results in variable levels. TMZ is stable at an acidic pH, allowing oral absorption, and has a broad biodistribution.

Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O6 and N7 positions of guanine.

8.1.4 Storage and Stability

As a solid, temozolomide is thermally stable and does not decompose when exposed to light. In solution, temozolomide undergoes rapid hydrolysis in a basic environment. The product label recommends storage at room temperature 25°C (77°F). Temozolomide should be stored at 20-25°C (68-77°F), excursions permitted between 15-30°C (59-86°F).

8.1.5 Dose Specifics

ARM A: 200 mg/m^2 po QD on days 1-5

ARM B: 200 mg/m^2 po QD on days 10-14

The temozolomide dose will be capped at 400 mg daily and is available as 5, 20, 100, 140, 180, or 250 mg capsules. The calculated dose by body surface area (BSA) will be rounded down to minimize the number of pills required.

8.1.6 Preparation

N/A

8.1.7 Route of Administration

Oral

8.1.8 Incompatibilities

N/A

8.1.9 Availability

Commercial supply

8.1.10 Side Effects

Hematologic: anemia, neutropenia, thrombocytopenia, aplastic anemia.

Constitutional: fatigue, anorexia, weight loss

Dermatologic: rash, pruritus, Stevens-Johnson-Syndrome

Gastrointestinal: nausea, vomiting, constipation, diarrhea, abdominal pain, stomatitis, dysphagia

Infections: PCP infection

Metabolic: hyperglycemia, liver or kidney abnormalities

Neurologic: headache, somnolence, insomnia, blurred vision

Oncologic: secondary malignancy

Psychiatric: anxiety, depression

8.1.11 Nursing/Patient Implications

8.1.11.1 Monitor CBC and platelet count prior to drug administration.

8.1.11.2 Symptom management of expected nausea, vomiting, photosensitivity, and mucositis within ≤ 3 months prior to treatment.

8.1.11.3 Ondansetron will be given as a premedication to prevent nausea 30-60 minutes prior to the temozolomide dose.

8.1.11.4 Temozolomide should be taken by mouth after fasting from solid food for two hours.

8.1.11.5 Temozolomide tablets must <u>not be</u> crushed and must be administered whole.

8.1.11.6 Temozolomide missed doses will not be made up, and patients should not double-up on missed doses during treatment. Do not repeat dose if vomiting occurs after dose is administered.

8.1.11.7 Liver function tests should be performed after each treatment cycle. For patients with significant liver function abnormalities the benefits and risks of continuing temozolomide should be carefully considered.

8.1.12 References

1. Temozolomide package insert.

8.2 Capecitabine

8.2.1 Other Names

Xeloda

8.2.2 Classification

Cytotoxic chemotherapy, anti-metabolite

8.2.3 Mode of Action

Capecitabine is a fluoropyrimidine carbamate that is an orally active prodrug of 5-fluorouracil. Normal cells, as well as tumor cells, metabolize 5- fluorouracil into 5-fluoro-2'deoxyuridinemonophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). Both are metabolites that cause cell injury by two different mechanisms. FdUMP and the folate factor, N5-10-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to inhibit the formation of thymidylate. This deficiency of thymidylate causes cell cycle division to halt. This is because thymidylate is necessary for thymidine triphosphate production, which is essential for DNA synthesis. FUTP works by incorporating itself into transcription in place of uridine triphosphate therefore interfering with RNA transcription and protein synthesis.

8.2.4 Storage and Stability

Capecitabine is supplied as biconvex, oblong film-coated tablets, available as 500 mg tablets (peach). Capecitabine is stored at 25°C, with excursions permitted to 15 to 30 °C.

8.2.5 Dose Specifics

ARM A: None

ARM B: 750 mg/m^2 po BID on days 1-14

The calculated total daily dose by body surface area (BSA) will be rounded down to the nearest 500 mg allow doses using 500 mg tablets.

8.2.6 Preparation

N/A

8.2.7 Route of Administration

Oral

8.2.8 Incompatibilities

N/A

8.2.9 Availability

Commercial supply

8.2.10 Side Effects

Hematologic: anemia, neutropenia, thrombocytopenia

Cardiovascular: Edema, venous thrombosis

Constitutional: fatigue, pyrexia, swelling in hands, feet or abdomen, pain, chest pain

Dermatologic: hand-foot syndrome, dermatitis, skin discoloration, alopecia

Gastrointestinal: diarrhea, nausea, vomiting, stomatitis, abdominal pain, gastrointestinal motility disorder, constipation, taste disturbance, upper GI inflammatory disorders, gastrointestinal hemorrhage, ileus

Hepatic: hyperbilirubinemia

Infections: bacterial or viral

Metabolic: appetite decreased, dehydration

Musculoskeletal: back pain, arthralgia

Neurologic: peripheral sensory neuropathy, headache, dizziness, insomnia

Ocular: eye irritation, vision abnormal

Psychiatric: mood alteration, depression

Pulmonary: dyspnea, cough, pharyngeal disorder, epistaxis, sore throat

Vascular: venous thrombosis

8.2.11 Nursing/Patient Implications

8.2.11.1 Monitor CBC and platelet count prior to drug administration.

8.2.11.2 Administer doses at least 8 hours apart.

8.2.11.3 Symptom management of expected nausea, vomiting, diarrhea, and hand-foot skin syndrome.

8.2.11.4 Capecitabine tablets should be swallowed with water within 30 minutes after a meal.

8.2.11.5 Capecitabine tablets are allowed to be crushed.

8.2.12 References

1. Capecitabine package insert

9. Statistical Considerations

9.1 Expected Accrual Pattern

While neuroendocrine tumors (NETs) are relatively rare in the population, the absence of standard treatment options has led to significant interest and rapid accrual to clinical trials in this disease in recent years. For example, the recently completed industry-sponsored RADIANT3 study accrued 410 patients with pancreatic NETs over a period of 21 months from 18 countries (83 sites) for an overall accrual rate of 19 patients per month. CALGB 80701, a randomized study of everolimus with or without bevacizumab in patients with advanced pancreatic NET opened in October 2010 and has accrued over 70 patients, with a current accrual rate of approximately 6 per month. CALGB 80701 targets a similar population to the currently proposed study and will likely complete accrual within the next year. Assuming participation of several cooperative groups within the U.S., we similarly expect to enroll approximately 6 patients per month to this trial. Accrual is expected to be complete within 2 years from study activation.

9.2 Treatment Assignment

Patients will be randomized with equal probability to treatment with single agent temozolomide or the combination of temozolomide and capecitabine using a stratified permuted blocks algorithm with stratification based on prior treatment with everolimus (Yes vs No), prior treatment with sunitinib (Yes vs No) and concurrent administration of octreotide (Yes vs No).

9.3 Statistical Design and Efficacy Monitoring

The primary endpoint of this trial is progression-free survival (PFS). Patient assessments will be made every 3 months.

This study will require a minimum of 138 patients (or a maximum of 145 patients to allow for 5% ineligibility) to be accrued at the rate of roughly 6 patients per month. With 23 months of accrual time and 13 months of follow-up (3 years total study time), this trial will have at least 81% power to detect a difference in median PFS between the treatment arms of 9 versus 14 months (hazard ratio of 0.64) using a two-sided log-rank test at the overall 0.20 significance level. The assumption of 9 months for the temozolomide arm is based on historical data of temozolomide alone and temozolomide-based regimens as described in the introduction. The assumption of 14 months for the combination arm is based a goal of improving treatment by 55% (which conservatively approximates the Strosberg PFS data of 18 months).

There will be two log-rank tests conducted, an interim analysis at 76% information (at 80 PFS events, projected to occur just after the end of the accrual period at 26 months) and a final analysis at 100% information (105 PFS events), projected to occur at 3 years from the start of accrual. The overall type I error will be controlled using an O'Brien-Fleming boundary function. Using this boundary, if the repeated two-sided 95% confidence interval on the hazard ratio does not contain the target alternative hazard ratio of 0.64, consideration will be given to declaring the study negative and reporting the results. If the interim log-rank test is positive, the study can be reported early before the projected end of the follow-up period.

Response rate (RR) will be a secondary endpoint. RR will be defined by revised RECIST criteria version 1.1 and include complete responses and partial responses. Prior studies of single agent temozolomide suggest that the response rate associated with single-agent temozolomide is 8-24%; however, overall response rates associated with other temozolomide-based regimens in this disease are between 30-40%. For the purposes of this study, we assume that single agent temozolomide will be associated with a response rate of 33%. Retrospective series of temozolomide/capecitabine have reported response rates of 59-70% in advanced pancreatic neuroendocrine tumors.

With 138 patients there will be at least 80% power to detect an absolute difference of 20% in the objective response rates (for example, between 33% and 53% true response rates) using a two-group Fisher's exact test at an overall two-sided 20% significance level. In addition, within each arm, a 90% confidence interval on the true objective response rate will be no wider than 21 percentage points. Overall survival will also be a secondary endpoint but power for overall survival comparisons will be limited.

9.4 Safety Monitoring

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Expedited reporting of certain adverse events is required through the CTEP-AERS system, which is monitored continuously with formal notifications monthly of unexpected grade 4 and 5 events. 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 at least 69 patients per treatment arm, a 90% confidence interval on any adverse event rate will be no wider than 21 percentage points and there is at least 87% probability of observing one or more rare events (3% true probability) in either treatment arm.

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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.

9.5 Gender and Ethnicity

Based on previous data from the neuroendocrine stratum of ECOG study E4298 the anticipated accrual in subgroups defined by gender and race/ethnicity is as follows:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	3	3	6
Not Hispanic or Latino	69	70	139
Ethnic Category: Total of all subjects	72	73	145
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	3	3	6
Native Hawaiian or other Pacific Islander	0	0	0
White	69	70	139
Racial Category: Total of all subjects	72	73	145

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.

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10. Imaging Studies

ECOG-ACRIN plan to bank CT images collected during the course of the study at the central ACR Imaging Core Laboratory. This data set of serial images from more than 130 patients with pancreatic NETs will serve as one of the largest NET image banks. For the ECOG-ACRIN E2211 trial, we plan to evaluate specific clinical data elements to associate images with treatment milestones and use these images to retrospectively evaluate internal imaging consistency methodologies, such as quality of images received, reproducibility, and compliance. In the future, the de-identified image bank may be used for additional research, such as retrospective reviews of disease or software validation. Patient identifiers will never be included in future research and no patients will be named in publications related to future research.

10.1 Standard-of-Care Imaging Time Points and Minimum Preferred Phases

10.1.1 All standard-of-care imaging studies (including CT, MRI, PET, perfusion CT, or any combination) of the abdomen and pelvis, including all phases completed, will be submitted to ACRIN per Section 10.2 instructions. Submission of chest images is optional.

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10.1.2 Standard practice imaging studies for the trial per E2211 procedures include:

- Pre-treatment baseline scan for eligibility assessment;
- Imaging studies during study-prescribed treatment—(e.g. CT scans or MRIs at the completion of cycles 3, 6, 9, and 12 (approximately every 12 weeks).
- Follow-up imaging studies—e.g. CT scans or MRIs approximately every 3 months for 3 years from randomization and 6 months for 3-5 years from randomization or until disease progression.

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10.1.3 Preferably, a minimum of three (3) image phases will be submitted (see below), as well as any perfusion CT sequences that may be performed as standard institutional practice:

- Preferred:
  - Late arterial phase through the abdomen;
  - Portal venous phase through the abdomen and pelvis;
  - Delayed (equilibrium) phase through the abdomen at 3 to 4 min after contrast administration;
- If performed per standard institutional practice:
  - Perfusion CT sequences of an area of interest is optional and should be performed according to site specific specifications if available at the participating institution.

10.2 Images Submission

10.2.1 For TRIAD Submission: The preferred image transfer method is via TRIAD, a software application that ACRIN provides for installation on a site's PC. One or several computers of choice within the institutional "firewall" and on the institutional network may be equipped with TRIAD software; Internet access is also required. The TRIAD

application can then be configured as a DICOM destination on either scanner(s) and/or PACS system for direct network transfer of study related images into the TRIAD directory. When properly configured, the TRIAD software anonymizes, encrypts, and performs a lossless compression of the images before they are transferred to the ACRIN image archive in Philadelphia. Once equipment-readiness has been determined, imaging personnel from ACRIN will coordinate installation and training for the software.

For more information, contact: TRIAD-support@phila.acr.org or call 215-940-8820.

10.2.2 For Submission Via Media: In the event that the transfer of image data is not available via TRIAD, images may also be sent on a CD/DVD-ROM to the ACRIN core lab for transfer to the image archive. All image data submitted to the ACRIN core lab must be in DICOM format.

10.2.3 The Imaging Transmittal Worksheet (ITW) must accompany all image submissions. PDF versions of the transmission worksheets, along with completion and submission instructions, are available on the ACRIN website.

10.2.4 Images may be mailed to:

American College of Radiology Imaging Network
ACR Imaging Core Laboratory
Attn: E2211
1818 Market Street 16th Floor
Philadelphia, PA 19103

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11. Specimen Submission Requirements

Diagnostic material from previously collected tissue (core biopsy or surgical specimen preferred over FNA) must be submitted for central diagnostic review and classification and for laboratory research studies. These studies are defined in Section 12. Peripheral blood is to be submitted from consenting patients for future research studies.

All specimens submitted on this trial must be entered and tracked using the ECOG-ACRIN Sample Tracking System (see Section 11.3). Any case reimbursements associated with specimen submissions to ECOG-ACRIN – designated laboratories will be determined only from data contained in STS.

Specimens are to be labeled clearly with the ECOG-ACRIN protocol number "E2211", patient initials, date and time of collection, and sample type.

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11.1 Specimen Preparation Guidelines

11.1.1 Tissue Samples

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 for the central pathology review may render case unevaluable but will not impact patient participation in the trial.

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

- All original stained diagnostic slides.

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  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:

  1. Contact the repository to discuss expedited review. They may request that materials be held until requested.

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  2. Upon submission, indicate need for expedited review in the appropriate comment field in STS.
  3. If submission is delayed, a copy of the pathology report must be submitted and it is requested that the delay or inability to submit the materials be indicated in STS.

- One representative diagnostic formalin-fixed paraffin-embedded **tumor block,** core biopsy or surgical specimen preferred.

  NOTE: If a block is unavailable for submission, submit the following:

  - Twenty (20) unstained slides 4µm thick
  - Two (2) 4mm cores.

If these criteria cannot be met, please contact the ECOG-ACRIN Central Biorepository and Pathology Facility (eacbpf@mdanderson.org) to obtain alternative submission requirements.

- Forms:

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  - A copy of the surgical (if appropriate) and pathology reports and Immunologic studies (if available). If tissue submissions are delayed, reports are still required to be submitted following registration.
  - Sample Tracking System Shipping Manifest

11.1.2 Peripheral Blood, ACD or EDTA

Blood specimens are to be submitted for future research studies from patients who answered "yes" to "I agree to provide additional blood for research."

Samples are not to be drawn until after patient has been randomized to treatment. Although collection prior to start of protocol treatment is preferred, the sample may be drawn at any time during study participation.

- Draw blood into two 10mL ACD or EDTA tubes. Invert gently eight to ten times to thoroughly mix the blood and anti-coagulant.
- Specimen may be shipped at ambient temperature the day of collection or frozen (at < -70ºC preferred). If frozen, specimens collected in glass vacutainers must be transferred to sterile cryovials prior to freezing. Plastic vacutainers may be frozen directly.

11.2 Shipping Procedures

All sample submissions are to be accompanied with an STS shipping manifest.

11.2.1 Submission Schedule

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).

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

11.2.1.2 Peripheral blood samples from multiple patients may be batched and shipped together. The samples are to be shipped as follows:

- Samples shipped at ambient are to be shipped with a cool pack. If collected Monday – Thursday then ship day of collection. Samples collected on Friday or a weekend are to be placed in a refrigerator and shipped Monday.

- 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.

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11.2.2 Shipping Address

Samples are to be shipped using the CBPF's FedEx account using the FedEx On-Line Services.

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

Access to the shipping account for specimen shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center can now only be obtained by logging into fedex.com with an account issued by the ECOG-ACRIN CBPF. 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 CBPF by email at eacbpf@mdanderson.org

11.3 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.

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Important: 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 ecog.tst@jimmy.harvard.edu.

Study Specific Notes

Generic Specimen Submission Form (#2981v2) will be required only if STS is unavailable at time of sample submission. Notify the laboratory of the shipment

by Faxing a copy of the completed form to the laboratory. Indicate the appropriate Lab on the submission form:

- ECOG-ACRIN CBPF

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

11.4 Use of Specimens in Research

Pathology materials will be distributed to investigators for the central diagnostic review and laboratory research studies defined in Section 12.

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

Specimens submitted will be processed to maximize their utility for current and future research projects. Tissue 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.

If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study. Pathology materials may be retained for documentation purposes or returned to the site. All other specimens will be destroyed per guidelines of the respective repository

11.5 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

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12. Laboratory Research Studies

Submission of tumor tissue for central review and research studies is mandatory (see Section 11). Representative tumor tissue samples will be processed and routed by the ECOG-ACRIN CBPF for use in the studies described below. The results of these studies are for the purposes of the trial only and will not be returned to the site or reported to the patient.

Priority of tissue use:

1. Pathology Review
2. MGMT status by IHC
3. MGMT status by promoter methylation

12.1 Pathology Review

The appropriate representative tumor tissue samples will be forwarded to Teri Longacre, MD for central diagnostic review and classification to confirm the diagnosis of low or intermediate grade pNET. This is a retrospective review to determine the evaluability of the patient's data for data analysis. The results of the review are for the purpose of the trial only and will not be returned to the site.

12.2 Evaluation of MGMT status by IHC

Mouse monoclonal antibody to MGMT will be used (1:25 dilution; clone MT 3.1; Lab Vision), a biotinylated secondary antibody (mouse IgG), and then avidin-horseradish peroxidase (Vectastain Elite ABC Kit; Vector Laboratories) according to the manufacturer's instructions. Immunohistochemical MGMT expression will be scored as either ''intact'' or ''deficient'' in tumor cells using a prospective classification scheme. Tumors will be scored as ''intact'' when there is nuclear staining for MGMT in any tumor cells. Tumors will be scored as ''deficient'' when there is a complete absence of nuclear staining for MGMT in all tumor cells. Non-neoplastic cells (lymphocytes, stromal cells, and endothelial cells) served as an internal positive control in all tissue sections. We will additionally use an external tissue array control slide with known negative tumor.

The assay will be performed in a CLIA certified lab under the direction of Teri Longacre, MD at Stanford University.

12.3 Evaluation of MGMT status by promoter methylation

DNA is purified from formalin-fixed paraffin embedded and then treated with bisulfite. Bisulfite treatment chemically converts unmethylated cytosines to uracil but does not affect methylated cytosine. Two PCR reactions are then performed using primers corresponding to bisulfite modified (unmethylated) or unmodified (methylated) MGMT promoter sequence. The products of the PCR reaction are analyzed by agarose gel electrophoresis. Methylation-specific PCR performed on paraffin-embedded tissue specimens is dependent on tissue quality and quantity. It is important that there is little tissue necrosis since amplification could otherwise be compromised. It is to be expected to frequently see amplification of both methylated and unmethylated MGMT promoter sequences in the same specimen, which likely represents heterogeneity among tumor cells and/or the presence in the specimen of non-neoplastic cells. Presence of promoter

methylation, which causes epigenetic silencing of the MGMT gene, a DNA repair gene on chromosome 10q26, is a positive predictive factor for chemotherapeutic response to alkylating agents.

The assay will be performed in a CLIA certified lab under the direction of Iris Schrijver M.D at Stanford University.

12.4 Statistical Considerations

From prior correlative studies in ECOG-ACRIN it is expected that about 75% of cases will provide tissue amenable to MGMT evaluation, accounting for samples not obtainable and assay yield among obtainable samples. From earlier studies in pancreatic neuroendocrine tumors it is also anticipated that the MGMT-deficiency rate is roughly 50% and MGMT-deficient tumors are expected to be associated with higher levels of objective tumor response to temozolomide based therapy. Assuming that the overall response rate is 41% (across both treatment arms, under the alternative hypothesis) and that roughly 104 eligible patients with samples are available, there will be at least 80% power to detect an absolute difference in response rates of 29% (for example, 55% versus 26% in the MGMT-deficient versus MGMT-intact groups, respectively) using a two-sided 5% level Fisher's exact test. If the true difference in response rates between MGMT-deficient and MGMT-intact tumors is larger, power will be higher (for example 90% power for a difference in response rates of 57% versus 24%) and if the overall treatment response rate is closer to the null hypothesis (overall 33% response rate in both arms), there will be at least 85% power for the same level of absolute response rate difference, 29%, between the MGMT-deficient versus MGMT-intact groups. The evaluation of MGMT by IHC and promoter methylation and correlation with progression-free and overall survival will be exploratory in nature. Furthermore, statistical power for MGMT deficiency by treatment arm interactions will be limited given the relatively small size of this trial and these analyses will also be exploratory.

12.5 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

13. Electronic Data Capture

Please refer to the E2211 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.

14. Patient Consent and Peer Judgment

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

15. References

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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 E2211
4. ECOG-ACRIN Generic Specimen Submission Form (#2981)

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Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)
- ECOG-ACRIN Generic Specimen Submission Form (#2981)

Instructions:

1. Submitted materials must be adequately labeled, including:
   Patient's name (last, first)
   Protocol number
   Protocol case number (the patient's ECOG-ACRIN sequence number
   Institution
2. Complete blank areas of the pathologist's instructional memo and forward it, along with the List of Required Material and, if used, the Generic Specimen Submission Form, to the appropriate pathologist.
3. The pathologist should return the required pathology samples and surgical pathology reports, along with the completed ECOG-ACRIN Generic Specimen Submission Form (#2981). If any other reports are required, they should be obtained from the appropriate department at this time.
4. Keep a copy of the submitted documents and the StS-generated shipping manifest for your records.
5. Double-check that ALL required forms, reports and pathology samples are included in the package to the Central Biorepository and Pathology Facility. (See appropriate List of Required Material.)
   Pathology specimens submitted WILL NOT be processed by the Central Biorepository and Pathology Facility until all necessary items are received.
   Mail pathology materials to:

   ECOG-ACRIN Central Biorepository and Pathology Facility
   MD Anderson Cancer Center
   Department of Pathology, Unit 085
   Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
   1515 Holcombe Blvd
   Houston, TX 77030
   Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
   Fax: 713-563-6506
   Email: eacbpf@mdanderson.org

   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 Central Biorepository and Pathology Facility by telephone 844-744-2420 or by email at eacbpf@mdanderson.org.

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List of Required Material

E2211: A Randomized Phase II Study of Temozolomide or Temozolomide and Capecitabine in Patients with Advanced Pancreatic Neuroendocrine Tumor

Pre-Treatment

1. Institutional pathology report ***(must be included with EVERY pathology submission)***.

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2. Institutional surgical report (if surgical materials are submitted) and immunological studies reports (if performed)
3. *ECOG-ACRIN Sample Tracking System (STS) generated shipping manifest*
4. Required path materials.

- All original stained diagnostic slides.

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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:

1. Contact the repository to discuss expedited review. They may request that materials be held until requested.
2. Upon submission, indicate need for expedited review on the 638 form AND in the appropriate comment field in STS.
3. If submission is delayed, a copy of the applicable reports (#2 and #3 above) must be submitted and it is requested that the delay to submit the materials be indicated in STS.

- One representative diagnostic formalin-fixed paraffin-embedded **tumor block,** core biopsy or surgical specimen preferred.

NOTE: If a block is unavailable for submission, submit the following:

- Twenty (20) unstained slides 4µm thick
- Two (2) 4mm cores.

I f these criteria cannot be met, please contact the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF)(eacbpf@mdanderson.org) to obtain alternative submission requirements.

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.

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

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MEMORANDUM

TO: _____
(Submitting Pathologist)

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

DATE: _____

SUBJECT: *Submission of Pathology Materials for E*2211*: A Randomized Phase II Study of Temozolomide or Temozolomide and Capecitabine in Patients with Advanced Pancreatic Neuroendocrine Tumor)*

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for pathology review and laboratory research studies.

Keep a copy of the submission for your records and return, 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 ECOG-ACRIN ACRIN Central Biorepository and Pathology Facility.

Blocks and slides submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies. Paraffin blocks will be returned for purposes of patient management upon written request. The original stained diagnostic slides will be returned upon completion of the review.

> 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.*

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility at 844-744-2420 or by email at eacbpf@mdanderson.org.

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address:_____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

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A Randomized Phase II Study of Temozolomide or Temozolomide and Capecitabine in Patients with Advanced Pancreatic Neuroendocrine Tumors

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 help of people like you who participate in clinical trials, we will achieve our goal of effectively treating and ultimately curing 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, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

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Appendix III

Patient Pill Calendar

Pill Calendar Directions

1. Take your scheduled dose of each pill as instructed by your doctor.
2. If you forget to take the pills, the missed pills will not be taken later.
3. Complete the appropriate calendar based on the arm you are assigned to (Arm A or Arm B).
4. Note the number of pills you take each day. If you develop any side effects/symptoms, please record them in the appropriate spot on your calendar. If you take any medication other than temozolomide or capecitabine, note them in the appropriate spot on your calendar.

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5. Do **not** take study medication on a day that has "XXXXX" on the calendar.
6. Please bring the empty bottle(s), any leftover pills and your pill calendar to your next clinic visit.

E2211 Patient Pill Calendar – Arm A

	Patient ID:_____ **Cycle #:_____** **Dose: Take _____# of capsules once daily**			
Cycle Day	**Date**	**Temozolomide**	**Time**	**Notes**
	MM/DD/YY	*# of Capsules Taken*	*XX:XX PM*	*Note any symptoms/side effects you experience or any medications you take besides Temozolomide.*
1				
2				
3				
4				
5				
6		**XXXXX**	**XXXXX**	
7		**XXXXX**	**XXXXX**	
8		**XXXXX**	**XXXXX**	
9		**XXXXX**	**XXXXX**	
10		**XXXXX**	**XXXXX**	
11		**XXXXX**	**XXXXX**	
12		**XXXXX**	**XXXXX**	
13		**XXXXX**	**XXXXX**	
14		**XXXXX**	**XXXXX**	
15		**XXXXX**	**XXXXX**	
16		**XXXXX**	**XXXXX**	
17		**XXXXX**	**XXXXX**	
18		**XXXXX**	**XXXXX**	
19		**XXXXX**	**XXXXX**	
20		**XXXXX**	**XXXXX**	
21		**XXXXX**	**XXXXX**	
22		**XXXXX**	**XXXXX**	
23		**XXXXX**	**XXXXX**	
24		**XXXXX**	**XXXXX**	
25		**XXXXX**	**XXXXX**	
26		**XXXXX**	**XXXXX**	
27		**XXXXX**	**XXXXX**	
28		**XXXXX**	**XXXXX**	

E2211 Patient Pill Calendar – Arm B

	Patient ID:_____Cycle #:_____ Dose: Take _____# of Temozolomide capsules once daily Dose: Take _____# of Capecitabine tablets twice daily					
Cycle Day	**Date**	**Capecitabine**	**Times**	**Temozolomide**	**Time**	**Notes**
	MM/DD/YY	*# of Tablets Taken*	*XX:XX AM/PM*	*# of Capsules Taken*	*XX:XX PM*	*Note any symptoms/side effects you experience or any medications you take besides Capecitabine or Temozolomide.*
1				XXXXX	XXX	
2				XXXXX	XXX	
3				XXXXX	XXX	
4				XXXXX	XXX	
5				XXXXX	XXX	
6				XXXXX	XXX	
7				XXXXX	XXX	
8				XXXXX	XXX	
9				XXXXX	XXX	
10						
11						
12						
13						
14						
15		XXXXX	XXXXX	XXXXX	XXXXX	
16		XXXXX	XXXXX	XXXXX	XXXXX	
17		XXXXX	XXXXX	XXXXX	XXXXX	
18		XXXXX	XXXXX	XXXXX	XXXXX	
19		XXXXX	XXXXX	XXXXX	XXXXX	
20		XXXXX	XXXXX	XXXXX	XXXXX	
21		XXXXX	XXXXX	XXXXX	XXXXX	
22		XXXXX	XXXXX	XXXXX	XXXXX	
23		XXXXX	XXXXX	XXXXX	XXXXX	
24		XXXXX	XXXXX	XXXXX	XXXXX	
25		XXXXX	XXXXX	XXXXX	XXXXX	
26		XXXXX	XXXXX	XXXXX	XXXXX	
27		XXXXX	XXXXX	XXXXX	XXXXX	
28		XXXXX	XXXXX	XXXXX	XXXXX	

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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.