ECOG-ACRIN cancer research group
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Rev. Add3

Randomized Phase II Study of Platinum and Etoposide versus Temozolomide and Capecitabine in Patients with Advanced G3 Non-Small Cell Gastroenteropancreatic Neuroendocrine Tumors including Poorly Differentiated Neuroendocrine Carcinomas and Well-Differentiated Neuroendocrine Neoplasms

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Addendum #3 – 9/19
Addendum #4

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Agents	IND#	NSC#	Supply
Cisplatin	IND Exempt Study	NSC 119875	Commercially available
Carboplatin	IND Exempt Study	NSC 241240	Commercially available
Etoposide	IND Exempt Study	NSC 141540	Commercially available
Temozolomide	IND Exempt Study	NSC 362856	Commercially available
Capecitabine	IND Exempt Study	NSC 712807	Commercially available

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	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 current 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) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

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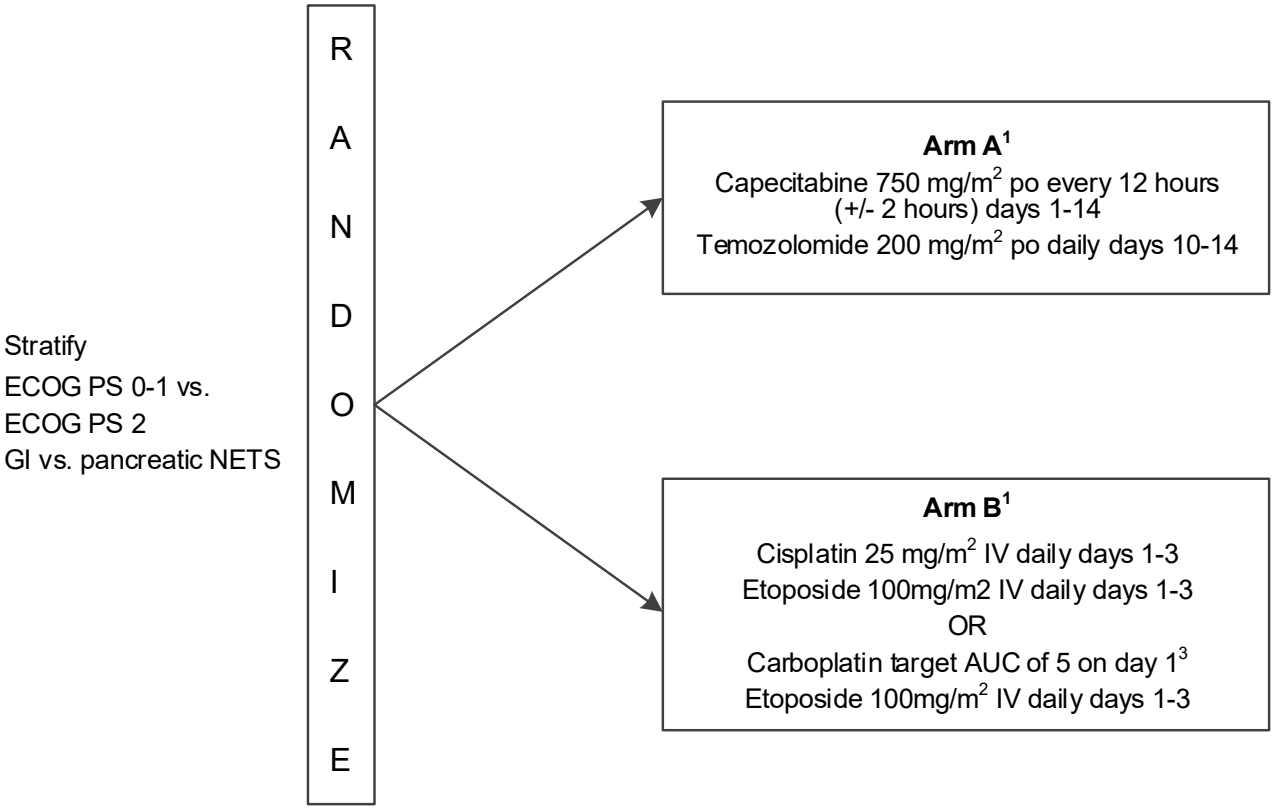
Schema



Accrual: 80
Cycle: Arm A-28 days
Arm B-21 days
All doses are based on actual body weight.
Images and radiology report submissions are required. See Section 4.4.5 for submission instructions and Section 10 for outline.

1. Treatment will continue until progression or unacceptable toxicity.
2. Capecitabine dose in mg/m^2 is PER DOSE and this dose should be taken every 12 hours.
3. Please refer to Section 5.1.2 for specific dose for Carboplatin

1. Introduction

1.1 Rationale for Selected Approach and Trial Design

Neuroendocrine carcinomas of the GI tract, while increasing in incidence, are uncommon with an age-adjusted annual incidence of 3.65/100,000 according to the Surveillance, Epidemiology, and End Results (SEER) database. Amongst these tumors, those with a high-grade (G3) are rare and account for approximately 11% of all gastroenteropancreatic neuroendocrine tumors. These are aggressive carcinomas that typically present at a late stage and have a dismal median overall survival of only 10 months (1). To date, and even for the current standard of care regimen, no prospective trial has been conducted to guide treatment for this disease and current treatment recommendations are extrapolated from the small cell lung cancer literature. Data pertaining to histologic classification and tumor biology are also extremely limited making the care of patients with this disease entity a significant challenge. Prospective studies evaluating potential treatment options with associated correlative studies to better understand the histologic and molecular features of these carcinomas are therefore desperately needed.

1.2 Population to be studied

The current WHO classification system defines G3 gastroenteropancreatic neuroendocrine carcinomas (NECs) as those with a Ki-67 of greater than 20% or a mitotic rate of > 20/10 high-powered fields (2). These are high grade malignant neoplasms that are histologically categorized as small cell, large cell or mixed neuroendocrine carcinomas with small cell carcinomas (accounting for approximately 35-43% of all lesions) being pathologically distinctive from the remaining classes of carcinomas (large cell or mixed neuroendocrine carcinomas) (3,4). Given the inclusion of a Ki-67 of greater than 20% up to 100%, this encompasses a broad range of proliferative indices that may in fact be more reflective of a very heterogeneous group. The Ki-67 labeling index has not been specifically evaluated amongst these subsets of G3 gastroenteropancreatic neuroendocrine carcinomas but amongst small cell lung cancer and neuroendocrine carcinomas of the lung it has been demonstrated that small cell lung cancer exhibits a significantly higher Ki-67 labeling index than large cell neuroendocrine carcinomas of the lung (5). Overall this would suggest that while all histologic subtypes are classified under one category (G3), small cell gastroenteropancreatic neuroendocrine carcinomas may be distinct from non-small cell gastroenteropancreatic neuroendocrine carcinomas. From a clinical standpoint, observations of heterogeneity within this population have also been made. In a study of patients with poorly differentiated gastroenteropancreatic neuroendocrine carcinomas (both small cell and non-small cell included) it was reported that patients not responding well to platinum based therapy in the front-line setting (the current standard of care), often responded better to temozolomide based therapy, an agent used more for the treatment of well differentiated neuroendocrine tumors. Patients responding to temozolomide based therapy, while meeting the overall criteria for a neuroendocrine carcinoma, had Ki-67 levels in the lower end of the spectrum (less than 60%) and were noted to have tumor specimens that stained positive immunohistochemically for chromogranin A as well as positive octreotide scans

(6). These features all suggest a lesion that may be more aligned with a well differentiated neuroendocrine tumor. A subsequent retrospective evaluation of 305 patients with poorly differentiated neuroendocrine carcinomas (again, both small cell and non-small cell histologies included) showed that using a Ki-67 of 55% as a cutoff, patients in the lower Ki-67 range (20-54%) had a poorer response to platinum based therapy as compared to patients in the higher Ki-67 range (55-100%), with response rates of 15% vs. 42% respectively. However patients in the lower Ki-67 range had an improved 30 month survival as compared to patients in the high Ki-67 range with 30 month survival rates of 23% and 7% respectively (4). These data suggest that although currently classified as one tumor type, G3 gastroenteropancreatic neuroendocrine carcinomas are heterogeneous and may warrant a different treatment approach, particularly carcinomas with non-small cell histology. It is important to note that while well-differentiated pancreatic primaries and other gastrointestinal primaries are treated utilizing different treatment approaches. For G3 lesions of either gastrointestinal or pancreatic origin, the treatment approach is the same.

1.3 Selection of cisplatin and etoposide

Historically, patients with G3 gastroenteropancreatic neuroendocrine carcinomas are treated similarly to patients with small cell lung cancer given the histologic similarities between these two diseases and this is reflected in the guidelines of the National Cancer Comprehensive Network (NCCN) (7). As a result, cisplatin and etoposide, the current standard front-line therapy for small cell lung cancer, is also the standard front-line treatment for patients with a G3 gastroenteropancreatic neuroendocrine carcinoma. There have been no randomized prospective studies assessing cisplatin and etoposide in G3 gastroenteropancreatic neuroendocrine carcinomas but this regimen has been evaluated in the front-line setting for treatment of G3 gastroenteropancreatic neuroendocrine carcinomas in two small studies (one prospective, n=18, one retrospective, n=41) with observed response rates of 42-67% and an associated overall survival ranging from 15-19 months (8,9). In addition to being small studies, the definition of a poorly differentiated carcinoma in these trials was not consistent with the criteria used today and likely included carcinomas with small cell histology. Even with limited data for platinum and etoposide for treatment of G3 gastroenteropancreatic neuroendocrine carcinomas, it is the standard of care and therefore will serve as the control arm for this study.

1.3.1 Clinical experience with cisplatin and etoposide (control arm)

Current standard therapy for G3 gastroenteropancreatic neuroendocrine carcinomas is derived in large part from the small cell lung cancer literature and the NCCN (National Comprehensive Cancer Network) guidelines defer recommendations regarding treatment of G3 GI neuroendocrine carcinomas to the management of small cell lung cancer (7). Standard therapy for small cell lung cancer involves treatment with cisplatin and etoposide. A phase II study of VP-16 (etoposide) and cisplatin was conducted in 11 patients with limited stage and 20 patients with extensive stage small cell lung cancer. Of 17 evaluable patients with extensive disease, 29% achieved a complete response and an additional 59% achieved a partial response for an overall response rate of 88%. This was

associated with a median duration of response of 26 weeks and a median survival time of 39 weeks (10). A subsequent randomized phase III study of standard dose vs. high dose etoposide in combination with cisplatin for patients with extensive stage small cell lung cancer showed no improvement with higher doses of etoposide but confirmed excellent response rates, reporting a complete response rate of 22% and a partial response rate of 61% for an overall response rate of 83%. This was associated with a median overall survival of 11 months (11). A randomized phase III study of cisplatin and etoposide vs. cisplatin and irinotecan in patients with extensive stage small cell lung cancer showed a complete response rate of 9.1% and a partial response rate of 67.5% in the cisplatin and etoposide group for an overall response rate of 76.6%. This was associated with a median overall survival of 9.4 months (12). Additional randomized phase III studies have evaluated the role of cisplatin and etoposide in small cell lung cancer (13-15) with reported response rates of 44%, 63% and 57% respectively and associated median progression free survival of 4.6, 5.2 and 6.3 months respectively. Based on these data, cisplatin and etoposide has been established as the front-line regimen in the treatment of *small cell lung cancer*.

To a lesser extent, cisplatin and etoposide have been evaluated in high grade GI neuroendocrine carcinomas and in none of these studies was the G3 definition applied. A phase II study of 18 patients with “anaplastic” neuroendocrine carcinomas reported an overall response rate of 67%, a median duration of regression of 8 months and a median overall survival of 19 months (8). The results of this study are limited by the use of both an outdated classification system and outdated response criteria. A retrospective study of 41 patients with a poorly differentiated neuroendocrine carcinoma reported a response rate of 42%, a progression free survival of 8.9 months and an overall survival of 15 months (9). In addition to being retrospective in nature, this study was limited by the inclusion of 21 (out of 41 total) patients with primary tumors involving the respiratory tract, mediastinum, head and neck or unknown primary site. A retrospective study of 258 patients with poorly differentiated neuroendocrine carcinomas of the GI tract treated with either cisplatin and irinotecan or cisplatin and etoposide reported a response rate of 27% and a median progression free survival of 4 months in the cisplatin and etoposide treated group (16). Finally, a retrospective study of 305 patients with poorly differentiated gastroenteropancreatic neuroendocrine carcinomas reported a response rate of 31% and a median progression free survival of 4 months in 252 patients receiving platinum containing front-line therapy (4). When combined with the data in small cell lung cancer, these studies have served as the backbone supporting the use of cisplatin and etoposide in the treatment of poorly differentiated/G3 gastroenteropancreatic neuroendocrine carcinomas. Using these reported results, we have estimated a progression free survival of 6 months for the cisplatin and etoposide containing control arm of this study.

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1.3.2 Substitution of carboplatin for cisplatin

Given the toxicities associated with cisplatin, carboplatin is standardly used as an acceptable alternative treatment per the Small Cell Lung Cancer NCCN guidelines (7). These two agents have been found to be equivalent in multiple studies including small phase II trials, a retrospective study and a meta-analysis (17-20).

1.4 Selection of temozolomide and capecitabine

Temozolomide as a single agent has been evaluated in two phase II studies. When administered as second or third-line treatment to 28 patients with G3 gastroenteropancreatic neuroendocrine carcinomas (as defined only by Ki-67 greater than 20%, tumor histologic subtype not reported) a response rate of 0% and a median overall survival of 3.5 months were observed (10). Several other studies, however, have demonstrated response to a temozolomide based regimen in both poorly differentiated and well differentiated settings. When administered to 64 patients with relapsed sensitive or refractory small cell lung cancer, a response rate of 22% and a median overall survival of 5.8 months were observed (11). A retrospective evaluation of patients with G3 gastroenteropancreatic neuroendocrine carcinomas treated with temozolomide +/- capecitabine +/- bevacizumab in the second-line setting showed a response rate of 33% and a median overall survival of 22 months (6), the best overall survival of any regimen evaluated in this disease type. A retrospective analysis of 29 patients with neuroendocrine neoplasms who received temozolomide and capecitabine was recently conducted where primary sites included the pancreas (14 patients), gastrointestinal tract (5 patients), lung (8 patients) and unknown (2 patients). Six of these patients had G3 lesions, 2 of which had a Ki-67 of 20-30%. Both of these patients had a partial response to therapy (12). Amongst patients with well differentiated pancreatic neuroendocrine tumors, a regimen of temozolomide and capecitabine appears very promising with a retrospective analysis of 30 patients receiving this treatment showing a response rate of 70% and a median progression free survival of 18 months (13). A small study reporting results in 28/38 planned patients with well differentiated neuroendocrine tumors (including 12 gastrointestinal carcinoid tumors and 11 pancreatic neuroendocrine tumors) receiving temozolomide and capecitabine demonstrates promising results; gastrointestinal carcinoids showed stable disease in 58%, a partial response in 33% and a complete response in 8% with a median progression free survival of > 22 months. In the pancreatic neuroendocrine tumor group, 55% showed stable disease, 45% had a partial response and median progression free survival was > 18.2 months (14). Also supporting the use of a temozolomide based regimen, a survey of international neuroendocrine experts conducted at the North American Neuroendocrine Tumor Society annual meeting in October, 2012 identified that of any regimen used for the second-line treatment of G3 gastroenteropancreatic neuroendocrine carcinomas, temozolomide and capecitabine was overwhelmingly the most popular at 41% of those surveyed. The next most commonly used regimens (streptozocin, irinotecan or platinum) had only 14% support comparatively. Clearly, the evidence base is scant and additional prospective study is required.

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1.4.1 Clinical experience with temozolomide and capecitabine

Multiple small studies of a variety of chemotherapy regimens have been conducted in the second line setting for the treatment of small cell lung cancer with very few promising results. Investigated regimens include both single agent and combination regimens of paclitaxel, gemcitabine, irinotecan, temozolomide, carboplatin, capecitabine and oxaliplatin (26-37). Treatment with carboplatin and paclitaxel showed the most promising response rate of 45-83% however median overall survival with this regimen has ranged from only 5.3-7.9 months (31). Even fewer studies have evaluated poorly differentiated/G3 gastroenteropancreatic neuroendocrine carcinomas specifically. A retrospective analysis of 25 patients with poorly differentiated gastroenteropancreatic neuroendocrine carcinomas who received a temozolomide-based regimen following treatment with a platinum based therapy was conducted. Patients received temozolomide alone, temozolomide plus capecitabine or either of these regimens plus bevacizumab and were reported to have an overall response rate of 33% with an associated progression free survival of 22 months (6), a progression free survival superior to any other second line therapy in either small cell lung cancer or poorly differentiated gastroenteropancreatic neuroendocrine carcinomas. As such, despite being retrospective data, a temozolomide-based regimen is accepted by many in the neuroendocrine community (and is used in actual practice) as an appropriate treatment option for second-line therapy in poorly differentiated/G3 gastroenteropancreatic neuroendocrine carcinomas. A recent retrospective analysis of 29 patients with neuroendocrine neoplasms who received temozolomide and capecitabine was recently conducted where primary sites included the pancreas (14 patients), gastrointestinal tract (5 patients), lung (8 patients) and unknown (2 patients). Six of these patients had G3 lesions, 2 of which had a Ki-67 of 20-30%. Both of these patients had a partial response to therapy. A total of 72% had either a partial response or stable disease, thereby demonstrating clinical benefit in patients with both poorly differentiated (G3) and well differentiated neoplasms (23).

As previously described, the G3 neuroendocrine carcinoma subset is likely comprised of a heterogeneous group of tumors as it contains neoplasms with both small cell and non-small cell histology. Particularly amongst the non-small cell subgroup, it is hypothesized that many non-small cell neoplasms may behave more like a well-differentiated tumor as many of the truly high grade, poorly differentiated carcinomas are often of small cell histology. In addition to demonstrating activity in poorly differentiated/G3 neuroendocrine carcinomas, temozolomide based regimens show promise in the well differentiated neuroendocrine tumors as well, particularly neuroendocrine tumors of the pancreas, which is also the most common site of origin amongst G3 gastroenteropancreatic neuroendocrine carcinomas (23, 38-40). In a phase II study of 29 patients with GI neuroendocrine tumors (pancreatic neuroendocrine tumors, carcinoids and paragangliomas, 28 well differentiated and 1

poorly differentiated) treated with temozolomide and thalidomide, an overall response rate of 25% was observed (45% in pancreatic neuroendocrine tumors, 7% in carcinoids). After a median follow-up period of 26 months, progression free survival and overall survival could not be reported (38). A phase II study of temozolomide and bevacizumab reported a response rate of 15% (33% in pancreatic neuroendocrine tumors, 0% in carcinoids) with an associated median progression free survival of 11.0 months (14.3 months in pancreatic neuroendocrine tumors, 7.3 months in carcinoids) (40). A retrospective study of 30 patients with pancreatic neuroendocrine tumors receiving a combination of temozolomide and capecitabine showed a response rate of 70% with a median progression free survival of 18 months (24). Finally, a small study reporting results of 28/38 planned patients with well differentiated neuroendocrine tumors (including 12 gastrointestinal carcinoid tumors and 11 pancreatic neuroendocrine tumors) receiving temozolomide and capecitabine demonstrates promising results; gastrointestinal carcinoids showed stable disease in 58%, a partial response in 33% and a complete response in 8% with a median progression free survival of > 22 months. In the pancreatic neuroendocrine tumor group, 55% showed stable disease, 45% had a partial response and median progression free survival was >18.2 months (25). These data have established a temozolomide based regimen as a reasonable consideration in the treatment of well differentiated pancreatic neuroendocrine tumors and emerging data suggests that this regimen is efficacious in well differentiated neuroendocrine tumors of non-pancreatic origin as well. To date, no other systemic chemotherapy has shown antitumor activity against both well differentiated and poorly differentiated gastroenteropancreatic neuroendocrine neoplasms.

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1.5 Rationale for proposed study

Based on both pathologic and clinical evidence, we believe that despite being categorized as a single entity, G3 gastroenteropancreatic neuroendocrine carcinomas are a heterogeneous group of tumors that may not all be best served by treatment with the current standard, platinum and etoposide, particularly tumors with non-small cell histology. Amongst the non-small cell subgroup, features outlined above suggest that some of these carcinomas may behave more like a well differentiated neuroendocrine tumor. Based on evidence that temozolomide and capecitabine show clinical activity in both well differentiated and the G3 population of gastroenteropancreatic neuroendocrine tumors/carcinomas, as well as consensus amongst the neuroendocrine treatment community that a temozolomide based regimen is a favored treatment option for this population and is already in use by many physicians, a regimen of temozolomide and capecitabine appears to be the most promising and warrants further investigation within this population. We therefore aim to conduct a randomized phase II study evaluating platinum (cisplatin or carboplatin) and etoposide (standard therapy) vs. temozolomide and capecitabine for the treatment of advanced G3 gastroenteropancreatic neuroendocrine carcinomas of the non-small cell subtype. We further plan to prospectively collect tissue specimens and patient images to conduct correlative molecular and imaging

analyses that may also improve our understanding of the underlying biology of this disease.

1.6 Selection of progression free survival as primary endpoint

Given the poor prognosis for this disease entity, overall survival was considered as a primary endpoint. However, we have chosen progression free survival as our primary endpoint for this study as it is anticipated that there will be a high rate of crossover to the opposite treatment arm at the time of disease progression, particularly with such limited treatment options for this disease. We will plan instead to evaluate overall survival as a secondary endpoint, the results of which will be more descriptive and exploratory in nature.

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1.7 Clinical Relevance of Study

Neuroendocrine tumors in general are rare and only 11% of them are neuroendocrine carcinomas categorized as a G3 lesion (1). As such, G3 neuroendocrine carcinomas are an orphan disease that has not been well studied and to date, *no prospective study* has been conducted in this patient population to evaluate either standard therapy (platinum and etoposide) or any other regimen in the front-line setting under the current WHO classification system. Current recommendations for treatment of this disease are largely based on the small cell lung cancer literature and this is also reflected in the National Comprehensive Cancer Network (NCCN) guidelines (7). While there are similarities histologically between these two diseases, there are also likely many differences, particularly when considering tumors with non-small cell histology. Given the paucity of data regarding G3 gastroenteropancreatic neuroendocrine carcinomas, further studies are very much in need.

While there are histologic similarities between small cell lung cancer and G3 gastroenteropancreatic neuroendocrine carcinomas, only 35-43% of these tumors have small cell histology with the remaining being of large cell or mixed histology (3). As data for treatment of this disease is extrapolated from the small cell lung cancer literature, it is unclear that the current standard of care (platinum and etoposide) is truly the most appropriate treatment regimen, particularly amongst the non-small cell population. Additionally, as described above, the current classification system for G3 gastroenteropancreatic neuroendocrine carcinomas encompasses a broad range of Ki-67 levels. Recent retrospective clinical data suggests that Ki-67 may influence response to treatment and impact survival suggesting an underlying pathologic heterogeneity under the umbrella of one diagnosis (4), however this has not been prospectively evaluated. A clearer understanding of both the biology of these carcinomas as well as their response to the proposed regimens, using an updated classification system and in the context of a large, prospective, randomized study has great potential to result in findings that could be practice changing.

This is the first attempt to conduct a prospective randomized study in G3 gastroenteropancreatic neuroendocrine carcinomas. As this is a rare disease, the conduct of a subsequent phase III study would be unlikely. The results of this study would represent the largest clinical experience gained in the treatment of G3 gastroenteropancreatic neuroendocrine carcinomas and therefore would likely be practice changing, particularly for the non-small cell variety of G3 gastroenteropancreatic neuroendocrine carcinomas.

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2. Objectives

2.1 Primary Objectives

2.1.1 To assess the progression free survival (PFS) of platinum (cisplatin or carboplatin) and etoposide versus the PFS of temozolomide and capecitabine in patients with advanced G3 non-small cell gastroenteropancreatic neuroendocrine carcinomas.

2.2 Secondary Objectives

2.2.1 To assess the response rate (RR) of platinum (cisplatin or carboplatin) and etoposide versus the RR of temozolomide and capecitabine in patients with advanced G3 non-small cell gastroenteropancreatic neuroendocrine carcinomas.

2.2.2 To assess the overall survival (OS) of platinum (cisplatin or carboplatin) and etoposide versus the OS of temozolomide and capecitabine in patients with advanced G3 non-small cell gastroenteropancreatic neuroendocrine carcinomas.

2.2.3 To evaluate the toxicities associated with the combination of temozolomide and capecitabine and the combination of platinum (cisplatin or carboplatin) and etoposide, respectively, in patients with advanced G3 non-small cell gastroenteropancreatic neuroendocrine carcinomas.

2.3 Laboratory Research Objectives

2.3.1 To assess the impact of each treatment regimen on PFS, RR and OS based on Ki-67 index in patients with advanced G3 non-small cell gastroenteropancreatic neuroendocrine carcinomas.

2.3.2 To assess the prognostic significance of well differentiated versus poorly differentiated non-small cell gastroenteropancreatic neuroendocrine tumors in relationship to survival and response to treatment.

2.3.3 To assess the agreement in Ki-67 status between that reported by institutional pathologist and that reported by central pathology review.

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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, M) _____

Physician Signature and Date _____

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 Patients must have a locally advanced and unresectable or metastatic gastroenteropancreatic neuroendocrine carcinoma that is either known or suspected to be of GI origin. Primary tumors arising from the lung, gynecologic organs or prostate are not permitted.

_____ 3.1.2 Patients must have pathologically/histologically confirmed tumor of non-small cell histology.

_____ 3.1.3 Patients must have a Ki-67 proliferative index of 20-100% OR at least 10 mitotic figures per 10 high powered fields

_____ 3.1.4 Patients 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 within 4 weeks prior to randomization and must be acquired by multiphasic CT or contrast MRI.

NOTE: PET-CT scans are allowed provided the CT portion of the exam is equivalent to a diagnostic CT scan and includes both oral and IV contrast.

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_____ 3.1.5 Patients may not have had any prior systemic therapy (chemotherapy, targeted therapy, PRRT) for this malignancy. Prior somatostatin therapy is permitted. Prior palliative radiation is permitted but radiated lesions may not be used for measurement.

_____ 3.1.6 Patients may not have received any of the protocol agents within 5 years prior to randomization.

_____ 3.1.7 Any prior surgeries must have been completed at least 4 weeks prior to randomization.

_____ 3.1.8 Patients must be at least ≥ 18 years of age.

_____ 3.1.9 Patients must have an ECOG performance status of 0-2.

_____ 3.1.10 Patients may not be receiving any other investigational agents while on study treatment.

_____ 3.1.11 Patients may not be receiving Coumadin while on treatment. Other anticoagulants are allowed.

_____ 3.1.12 Patients must have normal organ and marrow function as definded below within less than or equal to 14 days prior to randomization:

3.1.12.1 Leukocytes ≥ 3,000/mm^3

Leukocytes _____ Date: _____

3.1.12.2 Absolute neutrophil count ≥ 1,500/mm^3

Neutrophil count: _____ Date: _____

3.1.12.3 Hemoglobin ≥ 9 g/dL

Hemoglobin: _____ Date: _____

3.1.12.4 Platelets ≥ 100,000/mm3

Platelets: _____ Date: _____

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

ULN: _____ Bilirubin: _____ Date: _____

3.1.12.6 AST (SGOT)/ALT (SGPT) ≤ 2.5 X institutional ULN or (≤ 5 X institutional ULN if the patient has liver metastases).

ULN: _____ AST _____ Date: _____

ULN: _____ ALT _____ Date: _____

3.1.12.7 Serum creatinine ≤ 1.5 X institutional ULN and creatinine clearance ≥ 60 ml/min

ULN: _____ Creatinine: _____ Date: _____

NOTE: Creatinine Clearance must be calculated using the Cockcroft-Gault equation.

_____ 3.1.13 Patients must have a life expectancy of ≥ 12 weeks as determined clinically by the treating physician.

_____ 3.1.14 Patients with brain metastases (either remote or current) or presence of carcinomatous meningitis are not eligible

_____ 3.1.15 Patients with known DPD deficiency will be excluded as the use of capecitabine is contraindicated in these patients.

_____ 3.1.16 Patients must NOT have active or uncontrolled infection, symptomatic heart failure, unstable angina pectoris, cardiac arrhythmia or a serious psychiatric illness/social situation that would limit compliance with study requirements.

_____ 3.1.17 Patients with impaired decision making capacity may participate in the study if a legal authorized representative is available to consent.

_____ 3.1.18 Patients must NOT have a history of allergic reactions attributed to compounds of similar chemical or biochemical composition to cisplatin, carboplatin, etoposide, temozolomide or capecitabine.

_____ 3.1.19 Patients must NOT have absorption issues that would limit the ability to absorb study agents.

_____ 3.1.20 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: ____

_____ 3.1.21 Patients with symptomatic peripheral vascular disease are not eligible.

_____ 3.1.22 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, superficial bladder cancer, or breast cancer in situ.

  OR

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

  OR

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

  Date of last evidence of disease: _____

Rev. Add3 _____ 3.1.23 Women must not be pregnant or breast-feeding due to potential harm to the fetus from cisplatin, carboplatin, etoposide, 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 achieved menarche at some point 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female of child bearing potential? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.1.24 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.

_____ 3.1.25 Patients must be able to swallow pills.

_____ 3.1.26 Patients must be able to tolerate CT or MR imaging including contrast agents as required for the treatment and the protocol.

_____ 3.1.27 Patients who are known to have HIV or are on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with cisplatin, carboplatin, etoposide, temozolomide, and/or capecitabine. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

_____ _____

Physician Signature Date

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

4. Randomization Procedures

Cancer Therapy Evaluation Program Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, Rave, or TRIAD OR acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;

- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval.

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance). Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

CTSU Registration Procedures

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

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and

- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on Protocols in the upper left of your screen
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select ECOG-ACRIN, and protocol number EA2142;
- Click on Documents, select Site Registration, and download and complete the forms provided.

  NOTE: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory → Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Required Protocol Specific Regulatory Documents

1. 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.

2. 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:

You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website
- 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

NOTE: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

Patients must not start protocol treatment prior to randomization.

Treatment should start within ten working days after randomization.

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

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).
- A diagnostic specimen is available for central pathology review.

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

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. 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 Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

NOTE: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

4.1 Randomization

The following information will be requested for randomization:

4.1.1 Protocol Number

4.1.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics

- Gender
- Birth date (mm/yyyy)
- Race
- Ethnicity
- Nine-digit ZIP code
- Method of payment
- Country of residence

4.2 Eligibility Verification

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

4.3 Stratification Factors

Patients will be stratified by the following factors to ensure balance between arms.

4.3.1 ECOG PS 0-1 vs. ECOG PS 2

4.3.2 GI vs. Pancreatic NET

4.4 Additional Requirements

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

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

4.4.2 Biological specimens are to be submitted as indicated in Section 11.

4.4.3 Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata, site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required. To the hold Rave CRA role or Rave CRA (Lab Admin) role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

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

required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS 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 members' 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.

4.4.4 Imaging studies are to be submitted as indicated in Section 10 using TRIAD as indicated below.

4.4.5 Digital CT/MRI/PET Imaging Data Submission Using TRIAD

TRIAD is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account, and be registered as an A, AP, NPIVR or IVR. Please refer to CTEP Registration Procedures of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, site staff must hold the TRIAD Site User role on an NCTN or ETCTN roster. Individuals requiring a TRIAD Site User role should contact the person holding a primary role at the site for their affiliated NCTN or ETCTN roster.
- All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD, and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installations:

When a user applies for a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation

documentation can be found by following this link https://triadinstall.acr.org/triadclient/

This process can be done in parallel to obtaining your CTEP-IAM account username and password and RCR registration.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org or 1-703-390-9858.

4.5 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the EA2142 Forms Completion Guidelines.

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5. Treatment Plan

NOTE: No therapies (investigational or commercial agents) other than those described below may be administered with the intent to treat the patient's malignancy. No other investigational treatment may be given for any purpose while on study.

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NOTE: Patients whom have received prior somatostatin analogue therapy are permitted to stay on it if the treating physician feels that they are deriving clinical benefit from it for hormone mediated symptoms.

NOTE: An assessment of drug-drug interactions between patient's medication list and the assigned treatment should be conducted using updated package inserts prior to initiation of treatment.

All doses are based on actual body weight. If there is a < 10% change in weight, keep the doses the same. If there is a ≥ 10% change in weight, a new dosing weight should be set and used for dose calculations. If the newly calculated weight results in no change to the dose (for oral agents only), the same dose may be used if felt to be indicated by the treating physician.

5.1 Administration Schedule

5.1.1 Capecitabine and Temozolomide —Arm A

Cycle = 28 days (+/- 2 days)

- Capecitabine 750 mg/m^2 by mouth every 12 hours (+/- 2 hours) on days 1-14
- Temozolomide 200mg/m^2 by mouth once daily on days 10-14

NOTE: Please refer to the Patient Pill Calendar in Appendix III. Patients are required to return their completed Patient Pill Calendar at each clinic visit.

Premedication required: Ondansetron or an approved 5HT3 antagonist should be used as a premedication 30-60 minutes prior to temozolomide. Other anti-emetics, anxiolytics, and analgesics may be provided at physicians' discretion

Continue treatment until patient develops disease progression (as defined by Section 6.1.4) or unacceptable toxicity

Patients will need to be asked about other drugs they are taking at home such as OTC products, herbal medicines, tea, or other prescribed drugs. Patients should record this information on their Pill Calendar

5.1.1.1 Arm A Treatment Notes

Monitor CBC and platelet count prior to drug administration.

- The calculated total daily capecitabine dose by body surface area (BSA) will be used and treatement should be administered according to the following table Only 500 mg tablets will be used:

Dose: 750 mg/m^2 every 12 hours (or 1500 mg/m^2/day)		500 mg tabs	
Surface Area (m^2)	Total Daily Dose (mg)	# tabs in AM	# tabs in PM
1.2-1.5	2000	2	2
1.51-1.83	2500	3	2
1.84-2.16	3000	3	3
2.17-2.5	3500	4	3
2.51-2.83	4000	4	4

- Capecitabine should be taken morning and night, with at least 12 hours (+/-2 hours) between each dose. Capecitabine pills should be swallowed with water within 30 minutes after a meal. Capecitabine pills may not be crushed. Capecitabine missed doses will not be made up and patients should not double-up on missed doses during treatment.
- The temozolomide dose will be capped at 400 mg daily. The calculated dose by BSA will be rounded to the closest mg amount permitted within the confines of available pill sizes. Temozolomide should 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.

5.1.2 Cisplatin (or Carboplatin) and Etoposide—Arm B

Cycle = 21 days (+/- 2 days)

CBC will be monitored prior to day 1 of drug administration.

Premedication with ondansetron (or other 5HT3 antagonist) and dexamethasone prior to each chemotherapy administration (days 1-3) is required. Additional antiemetics, analgesics and anxiolytics may be used per the discretion of the treating physician. Pre- and post-treatment hydration may be administered per institutional standards.

If the treating physician chooses to use Aprepitant, when given once daily for 14 days as a 100 mg capsule with an oral contraceptive containing 35 mcg of ethinyl estradiol and 1 mg of norethindrone, this decreased the AUC of ethinyl estradiol by 43% and decreased the AUC of norethindrone by 8%. Women of childbearing potential using pregnancy contraception that includes ethinyl estradiol should not receive Aprepitant for the treatment of nausea/delayed emesis. Patients may change to a different method of contraception if they wish to use Aprepitant.

- Cisplatin 25 mg/m^2 daily x 3 days (days 1-3) to be administered per institutional guidelines.

OR

- Carboplatin target AUC of 5 once on day 1 to be administered per institutional guidelines

AND

- Etoposide 100mg/m^2 daily x 3 days (days 1-3) to be administered per institutional guidelines.

Continue treatment until patient develops disease progression (as defined by Section 6.1.4) or unacceptable toxicity.

NOTE: Treatment will be administered on an outpatient basis unless local institutional standard practice requires inpatient administration.

NOTE: CALVERT FORMULA FOR CARBOPLATIN DOSING:

Total Dose (mg) = (target AUC) x (GFR + 25)

For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance.

Round up any creatinine ≤ 0.6 mg/dL, to 0.6 mg/dL

Glomerular Filtration Rate (GFR) Estimation: Calculated creatinine clearance of ≥ 50 cc/min using the Cockcroft-Gault formula:

Males: $\frac{(140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}}$

Females: Estimated creatinine clearance for males x 0.85

With the Calvert formula, the total (final) dose of carboplatin is calculated in mg, not mg/m^2.

DO NOT exceed a dose of 150 mg per AUC or cap at 750 mg/AUC5.

NOTE: Choice of platinum agent will be per treating physician discretion. Once a platinum agent is picked, no changes are allowed.

5.2 Adverse Event Reporting Requirements

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NOTE: Starting April 1, 2018, all expedited adverse events reporting through CTEP-AERS are required to use CTCAE v5, however, this study will continue to utilize CTCAE v4 for routine adverse event reporting in Rave and dose modifications.

5.2.1 Purpose

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

- **Routine reporting:** Adverse events are reported in a routine manner at scheduled times during a trial using Medidata Rave.
- **Expedited reporting:** In addition to routine reporting, certain adverse events must be reported in an expedited manner for

timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

5.2.2 Terminology

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

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

- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Expectedness:** Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes, when either the type of event or the severity of the event is NOT listed in the protocol or drug package insert.

5.2.3 Reporting Procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). The 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

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- the AE Team at ECOG-ACRIN (857-504-2900)
- the FDA (1-800-FDA-1088)

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

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

documentation must be faxed to the FDA (800-332-0178) in the same timeframe.

CTEP 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.

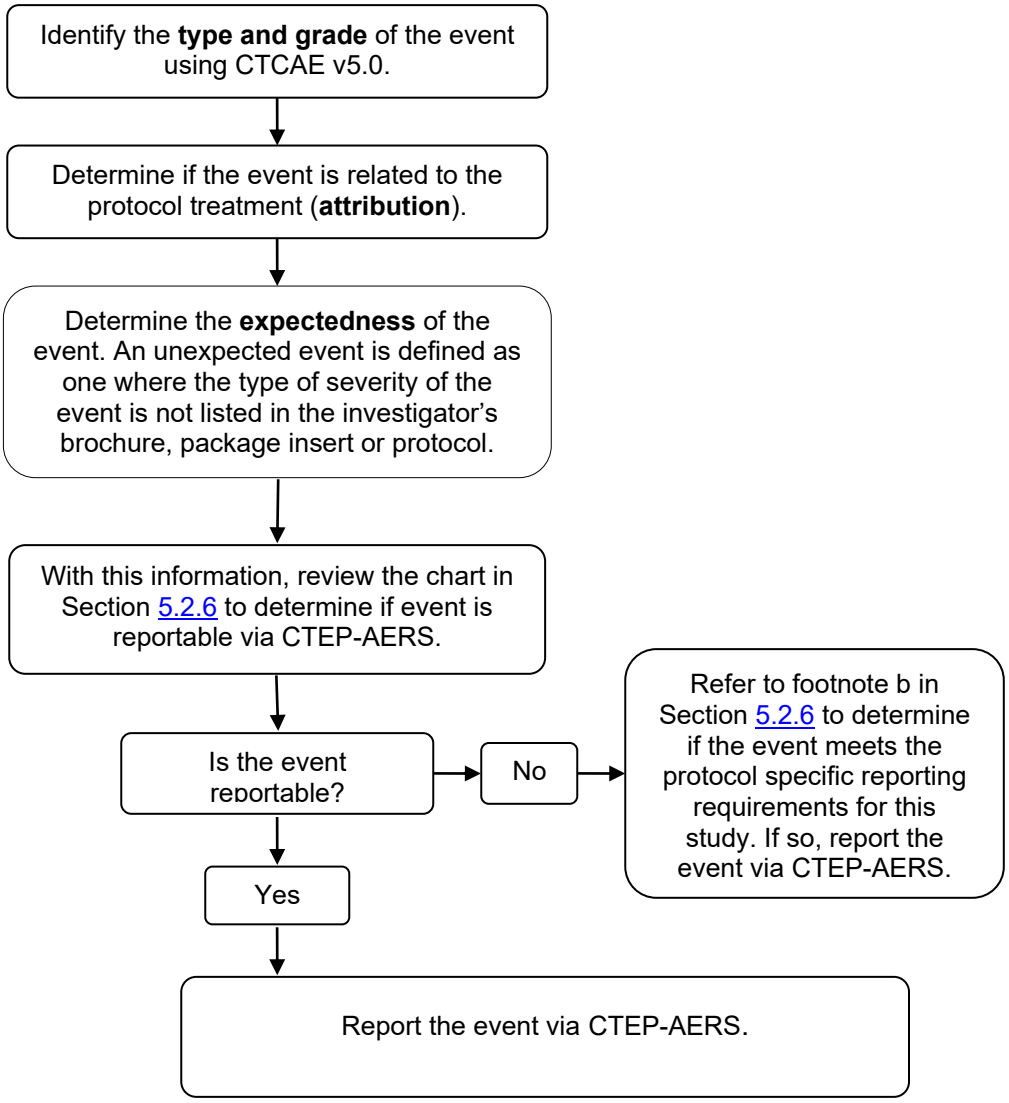
5.2.4 Determination of Reporting Requirements

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 EA2142 and outline the specific expedited adverse event reporting requirements for study EA2142.

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



5.2.6 Expedited Reporting Requirements for Arms A and B on protocol EA2142

Commercial Agents: Capecitabine, Temozolomide, Cisplatin, Carboplatin, and Etoposide

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	
Unrelated or Unlikely			7 calendar days	7 calendar days	See footnote (b) for special requirements.
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.

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a A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

NOTE: A death due to progressive disease should be reported as a Grade 5 "Disease progression" under the System Organ Class (SOC) "General disorder and administration site conditions". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

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

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

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG-ACRIN 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 ECOG-ACRIN Second Primary Form.

5.3 Dose Modifications

5.3.1 General

Dose reductions will be based on current dose. If dose reduction is required, reduction is permanent. Missed doses will not be made up. No dose escalation is permitted for any of the study drugs.

Dose will be modified for all drugs if there is ≥ 10% change in patient's weight while on study. For oral agents, particularly capecitabine, a new dose calculation may result in the same number of pills to be administered due to rounding issues.

Doses 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.

Patients may receive **a maximum of two** dose reductions per agent. If a third reduction is required, the patient should discontinue all protocol treatment. However, for Arm A, patients may discontinue one agent due to toxicity and continue the other on-study.

If different percentages of dose reductions for a specific drug are required because of two different types of toxicities, the greater percentage dose reduction should be undertaken.

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

NOTE: If patients have been off study treatment ≥ 4 weeks of next planned cycle start date, patients must discontinue protocol treatment.

NOTE: Starting cycles early is prohibited due to safety purposes.

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 Capecitabine Dose Modifications

Capecitabine will be initiated at 750 mg/m^2 orally twice daily x 14 days on a 28-day treatment cycle. Dose should be calculated as a total daily dose of 1500mg/m^2, then divided into two doses.

For all capecitabine dose modifications, if the protocol indicated that the dose should be reduced for subsequent administrations, a reduction of at least 500 mg (of the total daily dose) should be implemented even if the calculation including the dose reduction results in the same number of pills as was originally administered (example: if treated originally at 2500 mg daily, only 2000 mg daily may be administered if a dose reduction was called for).

5.3.2.1 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 platelets are ≥ 100,000/mm^3, resume at 20% dose reduction
≥ 1500/mm^3	and	≥ 100,000/mm^3	No dose modification

Mucositis, Diarrhea and Esophagitis

** Adequate medical management for these conditions should be implemented before a dose modification is made for one of these symptoms**

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 or 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.

5.3.2.2 Hyperbilirubinemia

If grade 3 or 4 hyperbilirubinemia occurs that is thought to be related to capecitabine, capcitabine should be held until the bilirubin improves to ≤ 3.0 x institutional ULN.

For grade 3 toxicity, resume capecitabine at 75% of the original starting dose for the first incident, 50% of the original starting dose for the second incident, and discontinue treatment permanently for the third incident. If the patient has already had a dose modification for another toxicity, the new dose level should be used as the baseline for making these adjustments.

For grade 4 toxicity, resume capecitabine at 50% of the original starting dose for the first incident and discontinue treatment permanently for any subsequent incident. If the

patient has already had a dose modification for another toxicity, the new dose level should be used as the baseline for making these adjustments.

5.3.2.3 Non-hematologic Toxicity

For other non-hematologic toxicities, dose reductions of capecitabine will be at the discretion of the investigator. A 20% dose reduction must be performed with each subsequent reduction. A maximum of 2 dose reductions can be performed.

5.3.3 Temozolomide Dose Modifications

- Dose reductions: For non-hematologic grade 3 and 4 AEs (except for nausea and vomiting as well as AEs unrelated to treatment) the dose should be reduced according to the Temozolomide Dose Level Table at the discretion of the investigator. Dose reductions for treatment day ANC and platelet counts should also be made according to the Dose Level Table below. Each dose reduction will be a 20% reduction from the prior level.
- Discontinuation: Also, except for nausea and vomiting, if any of the same non-hematologic grade 3 and 4 AEs that are at least possibly related to temozolomide recur after two reductions for that AE, then temozolomide will be stopped.

Temozolomide Dose Level Table	
Dose Level	Dose in mg/m^2
0	200
-1	160
-2	128

*Note this is a 20% dose reduction with each dose level.

5.3.3.1 Hematologic Toxicity

ANC (/mm^3)		Platelets (/mm^3)	% of Planned Temozolomide
≥ 1500/mm^3	and	≥ 100,000/mm^3	100%
750-1499/mm^3	or	50,000-99,999/mm^3	Hold*
< 750/mm^3	or	< 50,000/mm^3	Hold**

* Upon recovery to ANC ≥ 1,500/mm^3 and platelets to ≥ 100,000/mm^3, the dose level -1 will be administered (160 mg/m^2). Discontinue temozolomide dose if patients do not recover within ≤ 3 weeks. If patient was already receiving Temozolomide at the -1 dose level, reduce to the -2 dose (128 mg/m^2).

** Upon recovery to ANC ≥ 1,500/mm^3 and platelets to ≥ 100,000/mm^3, the dose level -2 will be administered (128 mg/m^2). Discontinue dose if patients do not recover within ≤ 3

weeks. If patient was already receiving Temozolomide at the -2 dose level, temozolomide should be discontinued.

5.3.3.2 Non-hematologic Toxicity

For non-hematologic toxicities, dose reductions of temozolomide will be at the discretion of the investigator. Dose reductions must follow the **Temozolomide Dose Level Table** above. A maximum of 2 dose reductions can be performed. For patients with significant liver function abnormalities the benefits and risks of continuing treatment should be carefully considered.

5.3.4 Cisplatin or Carboplatin Dose Modifications

- Dose reductions: For non-hematologic grade 3 and 4 AEs (except for nausea and vomiting as well as AEs unrelated to treatment) the dose should be reduced according to the Cisplatin/Carboplatin Dose Level Table at the discretion of the investigator. Dose reductions for treatment day (or within 2 days of treatment) ANC and platelet counts should also be made according to the Dose Level Table below.

NOTE: The etoposide will be held if platinum is held until a decision is made to skip platinum for the current cycle so that all drugs are kept on the same schedule.

- Discontinuation Also, except for nausea and vomiting, if any of the same non-hematologic grade 3 and 4 AEs that are at least possibly related to platinum recur after two reductions for that AE, then platinum will be stopped.
- A patient's protocol treatment will be discontinued if more than 2 cumulative dose reductions are necessary or if patients are unable to restart platinum within 3 weeks of interruption. Dose reductions will be permanent. Missed doses will be made up once toxicity is resolved per guidelines below.
- All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Cisplatin Dose Level Table	
Dose Level	Dose in mg/m^2 (days 1-3)
0	25
-1	20
-2	16

*Note this is a 20% dose reduction with each dose level.

Carboplatin Dose Level Table	
Dose Level	Dose in AUC (day 1)
0	5
-1	4

5.3.4.1 Recommended Dose Modifications

Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)	Recommended Dose Modifications to cisplatin any time during a cycle of therapy	Recommended Dose Modifications to carboplatin any time during a cycle of therapy
BLOOD AND LYMPHATIC SYSTEM DISORDER		
Anemia		
Grade 1 (Hgb < LLN-10.0 g/dL)	Maintain dose level.	Maintain dose level.
Grade 2 (Hgb < 10.0 g/dL - 8.0 g/dL)	Maintain dose level.	Maintain dose level.
Grade 3 (Hgb < 8.0 g/dL); transfusion indicated	Maintain dose level.	Maintain dose level.
Grade 4 (Life threatening consequences; urgent intervention indicated); related to study drugs	Discontinue study treatment.	Discontinue study treatment.
ANC decreased (Neutropenia)		
Grade 1 (ANC < LLN - 1.5 x 10^9/L)	Maintain dose level.	Maintain dose level
Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	Maintain dose level.	Maintain dose level
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L)	Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, and no fever. Then: - If resolved in ≤ 7 days, then maintain dose level - If resolved in > 7 days, then maintain dose level and consider prophylactic growth factor support per ASCO guidelines - If second occurrence, then ↓ 1 dose level for subsequent cycles.	Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, and no fever. Then: - If resolved in ≤ 7 days, then maintain dose level - If resolved in > 7 days, then maintain dose level and initiate prophylactic growth factor support per ASCO guidelines - If second occurrence, then ↓ 1 dose level for subsequent cycles.
Grade 4 (ANC < 0.5 x 10^9/L)	Omit dose of cisplatin until resolved to CTCAE ≤ Grade 1, then ↓ 1 dose level; additionally, consider prophylactic growth factor support per ASCO guidelines.	Omit dose of carboplatin until resolved to CTCAE ≤ Grade 1, then ↓ 1 dose level; additionally, consider prophylactic growth factor support per ASCO guidelines.
Febrile neutropenia		
Grade 3 (ANC < 1.0 x 10^9/L, single temperature of > 38.3°C or a sustained temperature of ≥ 38.0°C)	Omit dose of cisplatin, then - If resolved by ≤ 7 days, then ↓ 1 dose level and consider prophylactic growth factor support per ASCO guidelines. - If not resolved within 7 days despite appropriate management including full clinically indicated course of antibiotics, if indicated, discontinue patient from study treatment.	Omit dose of carboplatin, then - If resolved by ≤ 7 days, then ↓ 1 dose level and consider prophylactic growth factor support per ASCO guidelines. - If not resolved within 7 days despite appropriate management including full clinically indicated course of antibiotics, if indicated, discontinue patient from study treatment.
Grade 4	Discontinue study treatment.	Discontinue study treatment.
Platelet count decreased (Thrombocytopenia)		
Grade 1 (PLT < LLN - 75 x 10^9/L)	Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, then maintain dose level	Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, then maintain dose level
Grade 2 (PLT < 75 - 50 x 10^9/L)	Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level	Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level
Grade 3 (PLT < 50 - 25 x 10^9/L)	Omit dose of cisplatin until resolved	Omit dose of carboplatin until

Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)	Recommended Dose Modifications to cisplatin any time during a cycle of therapy	Recommended Dose Modifications to carboplatin any time during a cycle of therapy
	to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then then ↓ 1 dose level. - If resolved in > 7 days, then discontinue study treatment.	resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then then ↓ 1 dose level. - If resolved in > 7 days, then discontinue study treatment.
Grade 4 (PLT < 25 x 10^9/L)	Discontinue study treatment.	Discontinue study treatment
Bleeding		
Any bleeding (related to cisplatin or carboplatin) resulting in a transfusion requirement	Omit dose of cisplatin until no further bleeding has been observed. Continuation of study treatment may be considered.	Omit dose of carboplatin until no further bleeding has been observed. Continuation of study treatment may be considered.
INVESTIGATIONS – RENAL		
Serum creatinine		
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level.	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN)	Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1 or baseline, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in > 7 days, then ↓ 1 dose level.	Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1 or baseline, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in > 7 days, then ↓ 1 dose level.
Grade ≥ 3 (> 3.0 x ULN)	Discontinue study treatment.	Discontinue study treatment
INVESTIGATIONS – HEPATIC		
Blood Bilirubin [b] (for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only) For patients with total bilirubin ≥ grade 3, a CT scan or equivalent imaging procedure to exclude disease progression or potential other liver disease should be performed.		
Grade 1 (> ULN – 1.5 x ULN)	Maintain dose level.	Maintain dose level
Grade 2 (>1.5 – 3.0 x ULN)	Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in > 7 days, then ↓ 1 dose level.	Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in > 7 days, then ↓ 1 dose level.
Grade 3 (> 3.0 – 10 x ULN) or higher	Discontinue study treatment. **NOTE:** If CTCAE Grade 3 or 4 hyper-bilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g. review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the Investigator.	Discontinue study treatment. **NOTE:** If Grade 3 or Grade 4 hyperbilirubinemia is due to the indirect (unconjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓1 dose level and continue treatment at the discretion of the investigator.
AST or ALT		

Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)	Recommended Dose Modifications to cisplatin any time during a cycle of therapy	Recommended Dose Modifications to carboplatin any time during a cycle of therapy
Grade 1 and 2 (up to 5.0 x ULN)	Maintain dose level.	Maintain dose level.
Grade 3 (> 5.0 - 20.0 x ULN)	Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then maintain dose level. - If resolved in > 7 days, then ↓ 1 dose level.	Omit dose of carboplatin until resolved to Grade ≤1, then - If resolved in ≤ 7 days, then maintain dose level - If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (> 20.0 x ULN)	Discontinue study treatment.	Discontinue study treatment
NERVOUS SYSTEM DISORDERS		
Neurotoxicity		
Grade 1	Maintain dose level.	Maintain dose level.
Transient Grade 2 that improves to grade 1 on the day of planned therapy	Maintain dose level.	Maintain dose level.
Grade 2	Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level.	Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level.
Grade ≥ 3 or second occurrence of Grade 2	Discontinue study treatment.	Discontinue study treatment.
GI DISORDERS		
Diarrhea		
Grade 1	Maintain dose level, but initiate anti-diarrhea treatment as clinically indicated	Maintain dose level, but initiate anti-diarrhea treatment as clinically indicated
Grade 2	Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, including with appropriate management, then maintain dose level.	Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, including with appropriate management, then maintain dose level.
Grade 3	Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, initiate anti-diarrhea treatment, then - If resolved in ≤ 48 hours, maintain dose level. - If resolved in > 48 hours, then ↓ 1 dose level. For 2nd occurrence of diarrhea CTCAE Grade 3 for > 48 hours despite the use of anti-diarrhea treatment, discontinue study treatment.	Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, initiate anti-diarrhea treatment, then - If resolved in ≤ 48 hours, maintain dose level. - If resolved in > 48 hours, then ↓ 1 dose level. For 2nd occurrence of diarrhea CTCAE Grade 3 for > 48 hours despite the use of anti-diarrhea treatment, discontinue study treatment.
Grade 4	Discontinue study treatment.	Discontinue study treatment.
Nausea/Vomiting		
Grade 1	Maintain dose level, but initiate anti-emetic treatment.	Maintain dose level, but initiate anti-emetic treatment.
Transient Grade 2 that improves to grade 1 on the day of planned therapy	Maintain dose level.	Maintain dose level.

Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)	Recommended Dose Modifications to cisplatin any time during a cycle of therapy	Recommended Dose Modifications to carboplatin any time during a cycle of therapy
Grade 2	Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, initiate anti-emetic treatment, then maintain dose level.	Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, initiate anti-emetic treatment, then maintain dose level.
Grade 3	Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, initiate anti-emetic treatment, then: - If resolved in ≤ 48 hours, maintain dose level. - If resolved in > 48 hours, then ↓ 1 dose level.	Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, initiate anti-emetic treatment, then: - If resolved in ≤ 48 hours, maintain dose level. - If resolved in > 48 hours, then ↓ 1 dose level.
Grade 4	Discontinue study treatment.	Discontinue study treatment.
GENERAL DISORDERS		
Fatigue		
Grade 1 or 2	Maintain dose level.	Maintain dose level.
Grade 3	Omit dose of cisplatin until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, maintain dose level. - If resolved in > 7 days, discontinue patient from study treatment.	Omit dose of carboplatin until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, maintain dose level. - If resolved in > 7 days, discontinue patient from study treatment.
Grade 4	Discontinue study treatment.	Discontinue study treatment.
INFUSION REACTIONS		
Infusion reactions		
Grade 1 (Transient flushing or rash, fever < 38 °C [<100.4 °F]; intervention not indicated)	- Stop infusion - Treat per institutional guidelines. - May resume infusion (within 4 hours of initial start of infusion) at 50% of previous under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion. - Maintain dose level. - If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then do not resume infusion.	- Stop infusion - Treat per institutional guidelines. - May resume infusion (within 4 hours of initial start of infusion) at 50% of previous under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion. - Maintain dose level. - If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then do not resume infusion.
Grade 2 (Intervention or infusion interruption indicated; responds promptly to symptomatic treatment [e.g., antihistamines, NSAIDS, narcotics]; prophylactic medications indicated for ≤24 hrs)	- Stop infusion - Treat per institutional guidelines. - May resume infusion (within 4 hours of initial start of infusion) at 50% of previous under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion. - Maintain dose level. - If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then do not	- Stop infusion - Treat per institutional guidelines. - May resume infusion (within 4 hours of initial start of infusion) at 50% of previous under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion. - Maintain dose level. - If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then do not

Worst Toxicity CTCAE v4.0 Grade (unless otherwise specified)	Recommended Dose Modifications to cisplatin any time during a cycle of therapy	Recommended Dose Modifications to carboplatin any time during a cycle of therapy
	resume infusion.	resume infusion.
Grade 3 Prolonged [e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae [e.g., renal impairment, pulmonary infiltrates])	- Discontinue infusion immediately - Treat per institutional guidelines. - Discontinue patient from study.	- Discontinue infusion immediately - Treat per institutional guidelines. - Discontinue patient from study.
Grade 4 (Life-threatening; urgent intervention indicated)	- Discontinue infusion immediately - Treat per institutional guidelines. - Discontinue patient from study.	- Discontinue infusion immediately - Treat per institutional guidelines. - Discontinue patient from study.
OTHER ADVERSE EVENTS		
Grade 1 or 2	Maintain dose level of cisplatin or carboplatin. For intolerable grade 2 toxicity, may omit dose of cisplatin or carboplatin until resolved.	
Grade 3	Omit dose of cisplatin or carboplatin until resolved to CTCAE Grade ≤ 1, then ↓ dose level of cisplatin or carboplatin.	
Grade 4	Discontinue study treatment.	
NOTE: All of the above are general guidelines. The investigator may omit dose of drug, decrease dose level of drug, or remove any patient from study for any toxicity, if he/she believes that it is in the best interest of the patient. If a patient requires a dose delay of > 21 consecutive days of cisplatin or carboplatin then the patient must be discontinued from the study treatment. Patients who discontinue from the study for a study-related adverse event or an abnormal laboratory value must be followed at least once a week for 3 weeks and subsequently at 3-week intervals, until resolution or stabilization of the event, whichever comes first, unless stated otherwise.		

5.3.5 Etoposide Dose Modifications

- Dose reductions: For non-hematologic grade 3 and 4 AEs (except for nausea and vomiting as well as AEs unrelated to treatment) the dose should be reduced according to the Etoposide Dose Level Table at the discretion of the investigator. Dose reductions for treatment day (or within 2 days of treatment) ANC and platelet counts should also be made according to the Dose Level Table below. Each dose reduction will be a 20% reduction from the prior level.
- Discontinuation: Also, except for nausea and vomiting, if any of the same non-hematologic grade 3 and 4 AEs that are at least possibly related to study treatment recur after reduction for that AE, then etoposide will be stopped.

Etoposide Dose Level Table	
Dose Level	Dose in mg/m^2 (days 1-3)
0	100

Etoposide Dose Level Table	
-1	80
-2	64

*Note this is a 20% dose reduction with each dose level.

5.3.5.1 Hematologic Toxicity

ANC (/mm^3)		Platelets (/mm^3)	Modification
< 1500/mm^3	and/or	< 100,000/mm^3	Hold until ANC ≥ 1500/mm^3 and platelets are ≥ 100,000/mm^3, resume at 20% dose reduction*
≥ 1500/mm^3	and	≥ 100,000/mm^3	No dose modification

*This table applies to day of treatment (or within 2 days of treatment) hematologic toxicities.

*If ANC and platelet count recover within one week, resume therapy at 100%. If greater than 7 days to recovery, upon recovery to ANC ≥ 1,500/mm^3 and platelets to ≥ 100,000/mm^3, the dose level -1 will be administered (80 mg/m^2). Discontinue etoposide dose if patients do not recover within ≤ 3 weeks. If patient was already receiving Etoposide at the -1 dose level, reduce to the -2 dose (64 mg/m^2).

If already receiving treatment at the -1 dose level, upon recovery to ANC ≥ 1,500/mm^3 and platelets to ≥ 100,000/mm^3, the dose level -2 will be administered (64 mg/m^2). Discontinue dose if patients do not recover within ≤ 3 weeks. If patient was already receiving Etoposide at the -2 dose level, treatment should be discontinued.

Neutropenia or Febrile Neutropenia

For nadir neutropenia in the absence of fever or with fever that is successfully treated by oral antibiotics, there will be no dose adjustment. Filgrastim, sargramostim, or pegfilgrastim are allowed and should be administered according to ASCO guidelines (54). For treatment delays due to chemotherapy toxicities of more than 7 days, Etoposide should be dose-reduced according to the Etoposide Dose Level Table for all subsequent cycles of chemotherapy. For neutropenic fever (ANC < 500/mm^3) and temperature > 100.5F) requiring intravenous antibiotics, the doses of all chemotherapy drugs (cisplatin and etoposide) should be reduced by one dose level according to the Etoposide Dose Level Table and the Cisplatin Dose Level Table for the next cycle and all subsequent cycles. If counts to not recover within 4 weeks, discontinue all protocol therapy.

Thrombocytopenia

For grade 4 nadir platelet count decrease (thrombocytopenia) (platelets < 25,000/mm^3), the dose of Etoposide should be reduced by one dose level according to the Etoposide Dose Level Table for the next cycle and for all subsequent cycles of chemotherapy. If counts do not recover within 4 weeks, discontinue all protocol therapy.

Anemia

No dose reduction will be made for anemia. Patients should be supported per the treating physician's discretion. The use of blood transfusions for anemia will be allowed as indicated. The use of erythropoietin stimulating agents is not permitted.

5.3.5.2 Non-hematologic Toxicity

Gastrointestinal Toxicity, Nausea and Vomiting

All patients should receive antiemetics* to prevent nausea and vomiting. Steroids and 5-HT3 antagonists are required premedications but additional specific antiemetic therapy is left to the discretion of the treatment physician. If vomiting is severe, consider hospital admission and/or use of aprepitant if possible. Do not modify chemotherapy doses.

*Aprepitant, when given once daily for 14 days as a 100 mg capsule with an oral contraceptive containing 35 mcg of ethinyl estradiol and 1 mg of norethindrone, decreased the AUC of ethinyl estradiol by 43% and decreased the AUC of norethindrone by 8%. Women of childbearing potential using pregnancy contraception that includes ethinyl estradiol should not receive Aprepitant for the treatment of nausea/delayed emesis. Patients may change to a different method of contraception if they wish to use Aprepitant.

Hepatotoxicity

Bilirubin	Etoposide*
≤ 1.5 X ULN	100%
> 1.5 – 3.0 X ULN	50%
> 3.0 X - ≤ 5.0 ULN	30%
> 5 X ULN	Hold**

* Please note that the % dose administered is based on the original starting dose of etoposide (100 mg/m^2). If patient is at dose level -1 or -2, % should be based on reduced dose the patient is currently on, not original dose.

** For bilirubin greater than 5 X ULN it is recommended not to use etoposide for that cycle but this is at the discretion of the treating physician. If holding, repeat labs on a weekly basis for

up to 3 weeks until total bilirubin is ≤ 5 X ULN. The cisplatin dose should also be held if etoposide is held so that all drugs are kept on the same schedule. If bilirubin improves within 3 weeks to ≤ 5 X ULN, then resume treatment and use reduced dose per table above. If bilirubin does not improve to ≤ 5 X ULN within 4 weeks, discontinue protocol therapy.

Hypomagnesemia

Hypomagnesemia is not an indication for stopping therapy. Oral or parenteral magnesium supplementation is indicated for serum magnesium levels < 1.5 mEq/L.

Allergic Reactions

Discontinue all protocol treatment promptly if ≥ grade 3 anaphylaxis develops.

Suggested Management of Allergic Reaction:

In case of mild allergic symptoms (e.g., appearance of a localized or generalized pruritus), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

Patient experiencing significant allergic reaction should be managed according to local institutional standards. A combination of corticosteroids, antihistamines, nebulized respiratory therapy with beta (2) agonists and isotonic fluid support should be employed as appropriate based on patient's clinical condition.

For Grade 3 or Grade 4 symptoms: (Grade 3: severe reaction; prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]; Grade 4: life-threatening; pressor or ventilatory support indicated):

- Immediately discontinue chemotherapy infusion. Begin an i.v. infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration, 0.3 mg of a 1:1,000 solution for intramuscular administration, or 0.1 to 0.25 mg of a 1:10,000 solution slowly for i.v. administration, and/or diphenhydramine 50 mg i.v. with methylprednisolone 100 mg i.v. (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Cisplatin will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

Grade 3 or 4 Non-Hematologic Toxicity

If patient develops grade 3 or 4 non-hematologic toxicity attributed to protocol therapy but not detailed above, hold all therapy. These can be restarted if the toxicity has resolved to < grade 1 by the time of the next treatment. Doses of Etoposide should then be reduced according to the Etoposide Dose Level Table (taking into consideration the treatment dose used in the prior cycle).

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 or an equivalent 5HT3 antagonist is required as a premedication 30-60 minutes prior to temozolomide (Arm A).

5.4.3 Ondansetron or an equivalent 5HT3 antagonist and dexamethasone are required premedications prior to administration of platinum and etoposide (Arm B).

5.4.4 Hydration and/or diuresis for patients in Arm B is permitted and may be conducted per institutional guidelines.

5.4.5 In the event of platinum extravasation, apply a warm pack to reduce local discomfort and notify the treating physician of the extravasation. If indicated, restart peripheral IV in a larger vein.

5.4.6 For management of allergic reactions to cisplatin, see Suggested Management of Allergic Reactions under Section 5.3.5.2.

5.4.7 Patients must maintain adequate hydration and urinary output. Patients, on both arms, should be advised to increase oral fluid intake during treatment.

5.4.8 Aprepitant may be considered as an additional antiemetic for patients experiencing severe nausea and vomiting in Arm B. Caution with use of this medication should be considered as outlined in Section 5.1.2 in regard to female patients using oral contraceptive agents. All other antiemetic administration may be left to the discretion of the treating physician.

5.4.9 Appropriate supportive measures including Imodium and/or Lomotil should be implemented immediately to prevent dehydration should diarrhea develop.

5.4.10 The use of growth factors (filgrastim, sargramostim or pegfilgrastim) is permitted in both arms of the study and should be administered in accordance with ASCO guidelines (54).

5.4.11 The use of erythropoietin stimulating agents is NOT permitted. Anemia may be managed with blood transfusions as indicated.

5.4.12 Concomitant aminoglycoside antibiotic use should be avoided during platinum therapy until patient has fully recovered (i.e., at least 4 weeks from last dose of platinum).

5.4.13 Use of bisphosphonates or denosumab is allowed for patients with bone metastasis or hypercalcemia.

5.4.14 Anxiolytics and analgesics may be provided at physicians' discretion.

5.4.15 Supplemental pyridoxine (vitamin B6) is contraindicated in patients receiving cisplatin and may not be administered in patients on Arm B.

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 EA2142 Forms Packet.

5.5.2 Patient develops disease progression per Section 6.1.4.

5.5.3 Patient withdraws consent.

5.5.4 Patient experiences unacceptable toxicity

5.5.5 Non-protocol medical cancer therapies are administered. Localized surgical interventions or radiation intervention for a second primary malignancy may be permitted but should be discussed with the study chair prior to initiation.

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 8 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 not considered measurable.

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.

Chest X-ray

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

Conventional CT and MRI

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up 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.

FDG-PET

The role of FDG-PET response in this disease requires additional study. As such, new lesions identified on FDG-PET imaging may not be used to determine disease progression. FDG-PET will be interpreted visually (uptake above mediastinal blood pool will be interpreted as positive). Standardized uptake values (SUV) will be recorded in identified lesions for purposes of evaluation of response to treatment.

For correlative imaging studies, EORTC criteria will be used for the assessment of response to treatment by PET in solid tumors.

1. Progressive metabolic disease (PMD) to be classified as an increase in FDG tumor SUV of greater than 25% within the tumor region defined on the baseline scan, visible increase in the extent of FDG tumor uptake (20% in the longest dimension) or the appearance of new FDG uptake in metastatic lesions.
2. Stable metabolic disease (SMD) would be classified as an increase in tumor FDG SUV of less than 25% or a decrease of less than 15% and no visible increase in extent of FDG tumor uptake (20% in the longest dimension).
3. Partial metabolic response (PMR) would be classified as a reduction of a minimum of 15 ± 25% in tumor FDG SUV after one cycle of chemotherapy, and greater than 25% after more than one treatment cycle.

   Reporting would need to be accompanied by adequate and disclosed reproducibility measurements from each centre. An empirical 25% was found to be a useful cut-off point, but there is a need for a reproducibility analysis to determine the appropriate cut-offs for statistical significance. A reduction in the extent of the tumor FDG uptake is not a requirement for partial metabolic response.

4. Complete metabolic response (CMR) would be complete resolution of FDG uptake within the tumor volume so that it was indistinguishable from surrounding normal tissue.

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).

New effusion or ascites that appears during treatment should only be reported as a new lesion (and therefore progressive disease) if it has cytological confirmation of malignancy.

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/recurrence or non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient’s best response assignment will depend on the achievement of both measurement and confirmation criteria.

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

Target Lesions	Non-Target Lesions	New Lesions*	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.

Rev. 2/17

7. Study Parameters

7.1 Therapeutic Parameters

1. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done within 4 weeks prior to randomization.
2. Prestudy CBC (with differential and platelet count) and chemistries should be done ≤ 2 weeks before randomization.
3. Pregnancy testing (if applicable) should be done within 2 weeks of randomization.

	Prior to Randomization (Baseline)[1]	Day 1 of Each Treatment Cycle	Every 8 weeks	Post Treatment[9]
Tests and Observations				
Assessment of medical history[2]	X	X		X
Physical Examination[2,13]	X	X		X
Pulse, Blood Pressure[2]	X	X		
Height	X			
Weight and BSA calculation[2]	X	X		
Performance Status[2]	X	X		
Tumor Measurements[2]	X		X	X
Adverse Events Assessment[2]	X	X		X[10]
Pill Count/Diary		X[11]		
Laboratory and Imaging Studies				
CBC with Differential and Platelets[3]	X	X		
Serum Electrolytes and Liver Function Tests[2,4]	X	X		
Coagulation studies (PT, INR, aPTT)	X	X[12]		
Serum or Urine Pregnancy Test[5]	X			
Radiographic Studies[2,6]	X		X	X
Image Submissions[8]	X		X	
Biological Specimen Submissions[7].				
MANDATORY: Pre-trial FFPE tumor[7]	X			
Peripheral Blood, ACD vacutainer	X			

1. Baseline requirements must be assessed prior to randomization as outlined in Section 3. Blood tests must be performed ≤ 2 weeks prior to randomization. CT and/or MRI must be performed ≤ 4 weeks prior to randomization.
2. After Cycle 1, the following assessments may be scheduled with a +/- 3 day window; Assessment of medical history, Physical Examination, Pulse and Blood Pressure, Weight/BSA calculation, Performance Status, Tumor Measurements, Adverse Events Assessment, Serum Electrolytes and Liver Function, Radiographic Studies, including Images.
3. CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb and Hct required for protocol therapy must be done < 24 hours prior to the treatment cycle.
4. Serum Electrolytes and Liver Function Tests include Na+, K+, Cl-, bicarbonate, BUN, creatinine, glucose, Mg++, AST, ALT, alkaline phosphatase, total protein, albumin, total bilirubin and direct bilirubin.

Rev. Add3 5. All females of childbearing potential must have a negative [blood test or urine test] within 14 days prior to study registration to rule out pregnancy..

6. CT of the chest, abdomen and pelvis. If only MRI of the abdomen and/or pelvis is available, this can be substituted for CT of the abdomen and/or pelvis but CT of the chest should still be obtained. Contrast agents should be administered unless otherwise contraindicated. PET-CTs can be used, so long as the CT portion is of the same diagnostic quality and includes IV and oral contrast. The same screening technique used at baseline should be used for all subsequent follow-up scans. Even though dosing schedules are different in the two treatment arms, radiographic imaging should be obtained every 8 weeks by calendar while on protocol treatment.

7. Submit as outlined in Section 11. Mandatory diagnostic tumor tissue must be submitted for central diagnostic review and classification and ancillary laboratory research studies. Peripheral blood is to be submitted per patient consent. Submit to within 4 weeks following randomization.

Rev. Add3 8. Baseline and subsequent imaging studies should be submitted to the IROC Imaging Core Facility for central image banking < 4 weeks after each imaging time point. In addition to the CT/MRI scans, baseline and subsequent [^{18}F]-FDG PET scans, ^{68}Ga-PET scans and octreotide scans, if performed, should be submitted.

9. After completion of protocol treatment, monitor for adverse events for 30 days following discontinuation of treatment. Monitoring for survival, and scans should be performed every 3 months until patient is 2 years from randomization. Monitoring for survival and scans should be completed every 6 months if patient is 3-5 years from randomization. Once the patient progresses, adverse event assessments and scans no longer need to be performed but patients should be followed for survival (every 3 months until 2 years from randomization, every 6 months if 3-5 years from randomization).

10. Adverse Events Assessment is required 30 days after last dose of protocol therapy.

11. Note this is only required for patients randomized to Arm A.

12. Repeat coagulation studies only need to be followed in patients on anti-coagulant therapy and may be obtained within a +/- 3 day window along with serum electrolytes and liver function studies.

13. Baseline physical exam should be performed within 14 days of randomization.

8. Drug Formulation and Procurement

Capecitabine, temozolomide, cisplatin and etoposide will all be obtained commercially.

8.1 Capecitabine

8.1.1 Other Names

Xeloda

8.1.2 Classification

Cytotoxic chemotherapy, anti-metabolite

8.1.3 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, bine to tyhmidylate 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.

8.1.4 Storage and Stability

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

8.1.5 Dose Specifics

750 mg/m^2 orally by mouth twice daily on days 1-14 (Arm A)

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

8.1.6 Preparation

Available as 500 mg pills

8.1.7 Route of Administration

Capecitabine needs to be taken orally within 30 minutes after a meal

8.1.8 Incompatibilities

N/A

8.1.9 Availability

Commercially available

8.1.10 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, visual abnormalities

Psychiatric: mood alteration, depression

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

Vascular: venous thrombosis

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, diarrhea, and hand-foot skin syndrome

8.1.11.3 Administer doses at least 12 hours (+/- 2 hours) apart.

8.1.11.4 Capecitabine pills should be swallowed with water within 30 minutes after a meal.

8.1.11.5 Capecitabine pills may not be crushed.

8.1.12 References

1. Capecitabine package insert

8.2 Temozolomide

8.2.1 Other Names

Temodar

8.2.2 Classification

Cytotoxic chemotherapy, alkylating agent

8.2.3 Mode of Action

Temozolomide [8-carbamoyl-3-methylimidazo(5,1-d)-1,2,3,5-tetrazin-4(3H)-one] (Temodar) 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.

8.2.4 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 degrees C (77F). Temozolomide should be stored at 20-25 degrees C (68-77F), excursions permitted between 15-30 degrees C (59-86F).

8.2.5 Dose Specifics

200 mg/m^2 by mouth once daily on days 10-14 (Arm A)

The temozolomide dose will be capped at 400 mg daily and is available as 5, 20, 100, 140, 180, or 150 mg capsules. The calculated dose by body surface area (BSA) will be rounded down to minimize the number of pills required.

8.2.6 Preparation

N/A

8.2.7 Route of Administration

Oral

8.2.8 Incompatibilities

N/A

8.2.9 Availability

Commercially available

8.2.10 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

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8.2.11 Nursing/Patient Implications

8.2.11.1 Monitor CBC and platelet count prior to drug administration.

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

8.2.11.3 Ondansetron (or other approved 5HT3 antagonist) will be given as a premedication to prevent nausea 30-60 minutes prior to the temozolomide dose.

8.2.11.4 Temozolomide should be taken at night by mouth after fasting from solid food for two hours.

8.2.11.5 Temozolomide pills must <u>not</u> be crushed and must be administered whole.

8.2.11.6 Temozolomide missed doses will not be made up, and patients should not double-up on missed doses during treatment. Do no repeat dose if vomiting occurs after dose is administered.

8.2.11.7 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.

8.2.12 References

1. Temozolomide package insert

8.3 <u>Cisplatin</u>

8.3.1 Other Names

Cisdiaminedichloroplatinum, Cis-diaminedichloroplatinum (II), diaminedichloroplatinum, cis-platinum, platinum, Platinol, Platinol-AQ, DDP, CDDP, DACP, NSC 119875.

8.3.2 Classification

Cytotoxic chemotherapy, alkylating agent

8.3.3 Mode of Action

Inhibits DNA synthesis by forming inter- and intra-strand crosslinks. Other possible mechanism include chelation of DNA and binding to cell membranes thereby stimulating immune mechanisms.

8.3.4 Storage and Stability

Intact vials of cisplatin are stored at room temperature. Solutions diluted with sodium chloride or dextrose are stable for up to 72 hours at room temperature. Due to the risk of precipitation, cisplatin solutions should **not** be refrigerated.

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8.3.5 Dose Specifics

25 mg/m^2 on days 1-3 of each cycle to be administered per institutional standard. Cycle length is 21 days (Arm B).

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8.3.6 Preparation

Cisplatin to be mixed per institutional standard.

8.3.7 Route of Administration

Intravenous

8.3.8 Incompatibilities

Amsacrine, cefepime, gallium nitrate, mesna, piperacillin, sodium bicarbonate, thiotepa. Cisplatin may react with aluminum with is found in some syringe needles or IV sets, forming a black precipitate.

Compatibilities:

Admixture: Amphotericin-B, aztreonam, carmustine, cefazolin, cephalothin, droperidol, etoposide, floxuridine, hydroxyzine, ifosphamide, leucovorin, magnesium sulfate, mannitol, potassium chloride. Y-site: Allopurinol, bleomycin chlorpromazine, cimetidine, cyclophosphamide, dexamethasone, diphenhydramine, doxapram, doxorubicin, famotidine, filgrastim, fludarabine, fluorouracil, furosemide, ganciclovir, heparin, hydromorphone, lorazepam, melphalan, methotrexate, methylprednisolone, metoclopramide, mitomycin, morphine, ondansetron, paclitaxel, prochlorperazine, ranitidine, sargramostim, vinblastine, vincristine, vinorelbine.

Consult your pharmacist regarding specific concentrations.

8.3.9 Availability

Commercially available as a mg/mL solution in 50 and 100 mg vials.

8.3.10 Side Effects

Renal: A dose-related, cumulative renal tubular injury can occur; adequate hydration and diuresis usually minimize the risk. Salt-wasting nephropathy and/or orthostatic hypotension with hyporeninemic hypoaldosteronism can occur in up to 10% of patients.

Neurologic: A dose-related ototoxicity, manifested by high-frequency hearing loss and tinnitus occurs in about 30% of patients.

Paresthesias, decreased vibratory, position, and touch sensations are less common; particularly at cumulative doses < 400 mg/m^2.

Hematologic: mild leukopenia and thrombocytopenia occur in 25-30% of patients, but are rarely dose-limiting; anemia is less common. A potentially fatal hemolytic uremic syndrome has been reported.

Gastrointestinal: severe, dose-limiting nausea and vomiting occur in almost 100% of patients unless adequate antiemetic prophylaxis is given. Even with successful prophylaxis of acute nausea a delayed (72-96 hour) reaction, requiring addition therapy may occur. Anorexia and taste changes may also occur.

Hypersensitivity: allergic reactions are reported in up to 20% of patients. Symptoms include rash, facial edema, wheezing, hypotension and tachycardia. Severe anaphylaxis is rare.

Other: electrolyte wasting (magnesium, potassium and sodium), papilledema, optic neuritis, retrobulbar neuritis, diarrhea, mouth sores, hair loss, dizziness, dehydration, nail changes, fatigue, fluid retention, chills, lowered white blood cell counts, rash, muscle aches, joint pain, headache, confusion, loss of coordination, difficulty swallowing, indigestion, blood clotting in veins, fainting, seizures, difficulty urinating.

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8.3.11 Nursing/Patient Implications

8.3.11.1 Monitor CBC, platelet count, BUN and creatinine prior to drug administration.

8.3.11.2 Monitor for signs of ototoxicity or neurotoxicity.

8.3.11.3 Symptom management of expected nausea and vomiting. Ondansetron (or other 5HT3 antagonist) and dexamethasone will be given daily prior to chemotherapy administration. Additional antiemetics may be provided per physician discretion.

If the treating physician chooses to use Aprepitant, when given once daily for 14 days as a 100 mg capsule with an oral contraceptive containing 35 mcg of ethinyl estradiol and 1 mg of norethindrone, this decreased the AUC of ethinyl estradiol by 43% and decreased the AUC of norethindrone by 8%. Women of childbearing potential using pregnancy contraception that includes ethinyl estradiol should not receive Aprepitant for the treatment of nausea/delayed emesis. Patients may change to a different method of contraception if they wish to use Aprepitant.

8.3.11.4 Pre- and post-treatment hydration may be administered per institutional standards.

8.3.11.5 Diuretics may be ordered as needed per physician discretion.

8.3.11.6 Use of granulocyte colony stimulating factors are permitted.

8.3.11.7 Observe for signs of allergic reaction.

8.3.12 References

1. Alberts DS. Carboplatin versus cisplatin in ovarian cancer. Semin Oncol 1995;22 (5 Suppl 12):88-90.

2. Bonomi P. Platinum/etoposide therapy in non-small cell lung cancer. Oncology 1992;49 (Suppl 1):43-50.
3. Dabholkar M, Reed E. Cisplatin. Cancer Chemother Biol Response Modifiers 1993;14:86-97.
4. Fram RJ. Cisplatin and platinum analogues: recent advances. Curr Opin Oncol 1992;4:1073-9.
5. Garrow GC, Johnson, DH. Treatment of "good risk" metastatic testicular cancer. Semin Oncol 1992;19:159-65.
6. Markman M. Current status of intraperitoneal therapy for ovarian cancer. Curr Opinion Obstet Gynecol 1993;5:99-104.
7. Ozols RF, et al. Advanced ovarian cancer. Dose intensity. Ann Oncol 1993; (4 Suppl 4):49-56.
8. Saxman S. Salvage therapy in recurrent testicular cancer. Semin Oncol 1992;19:143-7.
9. Wheeler RH, Spencer S. Cisplatin plus radiation therapy. J Infusional Chemother 1995;5:61-6.

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8.4 Carboplatin

8.4.1 Other Names

Paraplatin®

8.4.2 Classification

Carboplatin (carboplatin injection) (platinum, diammine[1,1-cyclobutanedicarboxylato(2-)-O,O']-, (SP-4-2)) is a platinum coordination compound, used as an anti-neoplastic agent. It is a second-generation tetravalent organic platinum compound. It is a crystalline powder with the molecular formula of C6H12N2O4Pt and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5 to 7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

8.4.3 Mode of Action

Like cisplatin, carboplatin binds to DNA, thereby inhibiting DNA synthesis, in a cell cycle nonspecific manner. Carboplatin must first undergo activation to produce antineoplastic activity. Bidentate carboxylate ligands of carboplatin are displaced by water forming (aquation) positively charged platinum complexes, which bind to nucleophilic sites in DNA, such as the O-6 position on guanine. Carboplatin produces predominantly interstrand DNA crosslinks rather than DNA-protein crosslinks. Intrastrand crosslinks result from the formation of adducts between the activated platinum complexes of the drug and the N-7 atom (not exclusively) atom on guanine to produce 1,2 intrastrand links between adjacent guanine molecules, between neighboring guanine and adenosine molecules, or between neighboring guanine molecules. Interstrand cross-linking within the DNA helix also occurs. Platinum adducts may inhibit DNA replication, transcription and ultimately cell division.

8.4.4 Storage and Stability

Store intact vials at room temperature at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light. Further dilution to a concentration as low as 0.5 mg/mL is stable at room temperature (25°C) for 8 hours in NS or D_5W. Stability has also been demonstrated for dilutions in D_5W in PVC bags at room temperature for 9 days; however, the manufacturer recommends use within 8 hours due to lack of preservative. Multidose vials are stable for up to 14 days after opening when stored at 25°C (77°F) following multiple needle entries.

8.4.5 Dose Specifics

Carboplatin will be administered at AUC 5 IV on day 1 every 21 days (3 week cycles).

Calvert Formula for Carboplatin (AUC) Dosing

Total dose (mg) = target AUC (in mg/mL/minute) * GFR (in L/minute) + 25]

For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance.

Glomerular Filtration Rate (GFR) Estimation: Calculated creatinine clearance of ≥ 50 cc/min using the Cockcroft-Gault formula:

Males: $$\frac{(140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}}$$

Females: Estimated creatinine clearance for males x 0.85

With the Calvert formula, the total (final) dose of carboplatin is calculated in mg, not mg/m^2.

8.4.6 Preparation

Manufacturer's labeling states solution can be further diluted to concentrations as low as 0.5 mg/mL in NS or D_5W; however, most clinicians generally dilute dose in either 100 mL or 250 mL of NS or D_5W. Concentrations used for desensitization vary based on protocol. Hazardous agent; use appropriate precautions for handling and disposal. Needles or IV administration sets that contain aluminum should not be used in the preparation or administration of carboplatin; aluminum can react with carboplatin resulting in precipitate formation and loss of potency.

8.4.7 Route of Administration

Intravenous

8.4.8 Incompatibilities

Amphoterecin B chloesteryl sulfate complex. Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must NOT be used for the preparation or administration of carboplatin.

8.4.9 Availability

Carboplatin (Bristol-Myers Oncology Division) is commercially available in 50, 150, and 450 mg vials.

8.4.10 Side Effects

Hematologic: thrombocytopenia, neutropenia, leukopenia, anemia, more pronounced in patients with compromised renal function and heavily pretreated patients; may be cumulative.

Gastrointestinal: nausea, vomiting, treatable with moderate doses of antiemetics.

Dermatologic: rash, urticaria.

Hepatic: abnormal liver function tests, usually reversible with standard doses.

Neurologic: rarely peripheral neuropathy

Renal: elevations in serum creatinine, BUN; electrolyte loss (Na, Mg, K, Ca).

Other: pain, asthenia.

8.4.11 Nursing/Patient Implications

8.4.11.1 Monitor CBC and platelet count; nadir occurs at approximately day 21 with recovery by day 28-30.

8.4.11.2 Premedicate with antiemetics—evaluate effectiveness. Ondansetron (or other 5HT3 antagonist) and dexamethasone are required.

8.4.11.3 Monitor fluid status—maintain adequate hydration. Pre- and post-treatment hydration may be administered per institutional standards.

8.4.11.4 Assess skin/mucous membranes.

8.4.11.5 Assess for signs of peripheral neuropathy—coordination, sensory loss.

8.4.12 References

1. Calvert AH, et al. Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol 1989; 7:1748-1756.
2. Woloschuk DMM, Pruemer JM, Cluxton RJ. Carboplatin: A new cisplatin analog. Drug Intell Clin Pharm 1988; 22:843-849.
3. Christian MC. Carboplatin. In: Principles and Practice of Oncology, PPO Updates 1989; 3(11):1-16.

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8.5 Etoposide

8.5.1 Other Names

VP-16, VePesid, VP-16-213, EPEG, epipodophyllotoxin, NSC # 141540.

8.5.2 Classification

Cytotoxic chemotherapy, podophyllotoxin derivative.

8.5.3 Mode of Action

Etoposide inhibits the enzyme topoisomerase II, nucleoside transport and incorporation, and causes DNA breakage.

8.5.4 Storage and Stability

The injection should be stored at room temperature; the capsules must be refrigerated (2-8 degrees C). Following dilution in 0.9% sodium chloride or 5% dextrose to concentrations of 0.2-0.4 mg/mL the drug is chemically stable for 96 and 48 hours in the refrigerator and room temperature respectively (?). Bristol-Myers in-house data indicate that etoposide may be stable in 5% dextrose or normal saline for 24 hours (0.6 mg/mL), 4 hours (1 mg/mL), and 2 hours (2 mg/mL).

8.5.5 Dose Specifics

100 mg/m^2 on days 1-3 of each cycle per institutional standards. Cycle length is 21 days (Arm B).

8.5.6 Preparation

Etoposide to be prepared per institutional standard.

8.5.7 Route of Administration

Intravenous

8.5.8 Incompatibilities

Etoposide is compatible with cisplatin 200mg/mL in D5½NS or NS for 24 hours when protected from light. Addition of mannitol and/or potassium chloride reduces stability to 8 hours in NS, but remains stable for 24 hours in D5½NS in 5%; also compatible with cytarabine and daunorubicin.

8.5.9 Availability

Commercially available

8.5.10 Side Effects

Hematologic: leukopenia, dose-related, primarily granulocytopenia; nadirs within 7-14 days and recover within 20 days of administration; thrombocytopenia, uncommon; anemia.

Dermatologic: alopecia is generally mild, reversible and is reported to occur in 20-66% of patients although some patients develop total baldness; rarely rash, rarely severe pruritus, rarely radiation recall reaction, phlebitis, local pain at injection site, rarely pigmentation.

Gastrointestinal: nausea and vomiting, relatively uncommon, but more frequent with oral dosing; anorexia in 10-13% of patients; stomatitis, rarely with conventional doses, more common and more severe in patients who have received radiation to the head and neck and with high doses (e.g., bone marrow transplantation); abdominal pain,

diarrhea, aftertaste, parotitis, dysphagia, and constipation occur rarely.

Hypersensitivity: rarely anaphylaxis.

Hepatic: hyperbilirubinemia and increase transaminase levels, usually mild, transient and more common in high dose protocols.

Cardiovascular: transient hypotension, associated with rapid administration; rarely transient hypertension rarely; other cardiovascular events (e.g., congestive heart failure) thought to be related to large amounts of sodium chloride administered with the drug.

Neurologic: peripheral neuropathy, somnolence, fatigue, headache, vertigo, transient cortical blindness (all rarely); transient confusion with high doses, perhaps due to the alcohol-containing vehicle.

Other: rarely fever, muscle cramps, metabolic acidosis, hyperuricemia.

8.5.11 Nursing/Patient Implications

8.5.11.1 Monitor CBC and platelet count prior to drug administration.

8.5.11.2 Advise patient of possible alopecia. Instruct how to obtain wig, hairpiece, etc.

8.5.11.3 Observe for possible phlebitis at injection site or burning pain with infusion.

8.5.11.4 Monitor for rare anaphylactoid reaction.

8.5.11.5 Administer antiemetics as indicated.

8.5.12 References

1. van Maanen JMS, *et al.* Mechanism of action of antitumor drug etoposide: A review. J Natl Cancer Instit 1988; 80:1526-1533.
2. Stewart CF, Hampton EM. Stability of cisplatin and etoposide in intravenous admixtures. Am J Hosp Pharm 1989; 46:1400-1404.
3. Seargeant LE, *et al. In vitro* stability and compatibility of daunorubicin, cytarabine and etoposide. Cancer Treat Rep 1987; 71:1189-1192.
4. Fleming RA, *et al.* Etoposide: An update. Clin Pharm 1989; 8:274-293.
5. O'Dwyer PJ, *et al.* Etoposide, current status of an active anticancer drug. N Engl J Med 1985; 312:692-7

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9. Statistical Considerations

9.1 Endpoints

Primary Endpoint; Progression-Free Survival

Secondary Endpoint; Response Rate, Overall Survival, Toxicity

9.2 Revised statistical plan after Spring 2019 DSMC recommendation (July 2019)

Sample size with power justification

Accrual on this study has been lower than expected, averaging 1-2 patients per month. The ECOG-ACRIN DSMC reviewed this study in Spring 2019 and made the recommendation to modify the statistical plan to reduce the required power of the study to 80% in order to achieve a more realistic sample size and timeframe. Therefore, a total of 80 patients will now be the accrual target to achieve 78 randomized eligible cases. The study seeks to establish an improvement in the primary endpoint, which is defined as a 67% improvement in median progression-free survival (PFS) from 6 months in the control arm (Arm B) to 10 months in the experimental arm (Arm A). The study is now designed to have 80% power for this 40% reduction in the hazard rate with 71 PFS events at full information which is now expected to occur after 75 months of accrual and 7 additional months of follow-up. The primary comparison remains a log-rank test at a one–sided significance level of 0.10. Under exponential distributions the hypothesized reduction corresponds to 1-year progression-free survival of 44% in Arm A versus 25% in Arm B.

Analysis plan including plans for formal interim analysis

The primary analysis set will include all randomized eligible patients. Progression-free survival (PFS) is defined as time from randomization to documented progression or death without progression. Patients without documented progression or death reported will be censored at the time of the last documented disease evaluation. In the secondary analyses, overall survival (OS) is defined as time from randomization to death from any cause, censoring cases who are alive at the date of last contact. Kaplan-Meier estimates will be used for event-time distributions. PFS and OS by arm will be compared using one-sided stratified log-rank tests. Stratified Cox's proportional hazards models will be used to estimate hazard ratios. Response rate (complete response or partial response) and toxicity are also secondary endpoints. Response rate will be analyzed using a Fisher's exact test at a one–sided significance level of 0.10.

Patient demographics and disease characteristics will be compared using two-sample t-tests or Fisher's exact tests as appropriate. We will also conduct exploratory subset analyses with respect to PFS, OS, and response rate to evaluate the prognostic significance of Ki-67 with regard to these clinical endpoints.

Toxicity will be evaluated among all treated patients regardless of eligibility and interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. With 39 eligible patients per arm, the study will have sufficient precision to provide 90% confidence interval on toxicity that will be no wider than 28%. For rare toxicities with 4% true probability, there will be 80% probability of observing

one or more toxicities on either treatment arm. Formal comparison of toxicity rates between the arms is not a goal of this trial and the sample size will provide sufficient power for detecting only relatively large differences in adverse events.

This study will include one interim analysis of PFS for efficacy at approximately 48 months from the start of accrual (possibly near April 2020), which should correspond to 36 failures under the alternative hypothesis or 50% information time). A log rank test using an O'Brien-Fleming boundary will be conducted and under the alternative hypothesis there is probability of 0.29 that the efficacy boundary will be crossed. Regarding futility, if at the interim analysis the estimated hazard ratio for experimental/control is ≥1 the study will be reported as negative. If the estimated hazard ratio is less than 1 but the efficacy boundary is not crossed, the study will have its final analysis at 82 months of study. Results of the interim analysis will be presented to the ECOG-ACRIN Data Safety Monitoring Committee (DSMC) when appropriate.

9.2.1 Original statistical plan (prior to July 2019 amendment)

9.2.1.1 Sample size with power justification

A total of 126 patients will be needed to accrue 120 randomized eligible cases. The study seeks to establish an improvement in the primary endpoint, which is defined as a 67% improvement in median progression-free survival (PFS) from 6 months in the control arm (Arm B) to 10 months in the experimental arm (Arm A). The study is designed to have 90% power for this 40% reduction in the hazard rate with 120 eligible patients and 105 PFS events (at full information) which are expected to occur with 30 months of accrual at 4 patients per month and 12 additional months of follow-up, using a log-rank test at a one–sided significance level of 0.10. Under exponential distributions the hypothesized reduction corresponds to 1-year progression-free survival of 44% in Arm A versus 25% in Arm B.

9.2.1.2 Analysis plan including plans for formal interim analysis

The primary analysis set will include all randomized eligible patients. Progression-free survival (PFS) is defined as time from randomization to documented progression or death without progression. Patients without documented progression or death reported will be censored at the time of the last documented disease evaluation. In the secondary analyses, overall survival (OS) is defined as time from randomization to death from any cause, censoring cases who are alive at the date of last contact. Kaplan-Meier estimates will be used for event-time distributions. PFS and OS by arm will be compared using one-sided stratified log-rank tests. Stratified Cox's proportional hazards models will be used to estimate hazard ratios. Response rate (complete response or partial response) and toxicity are also secondary endpoints.

Response rate will be analyzed using a Fisher's exact test at a one–sided significance level of 0.10.

Patient demographics and disease characteristics will be compared using two-sample t-tests or Fisher's exact tests as appropriate. We will also conduct exploratory subset analyses with respect to PFS, OS, and response rate to evaluate the prognostic significance of Ki-67 with regard to these clinical endpoints.

Toxicity will be evaluated among all treated patients regardless of eligibility and interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. With 63 patients per arm, the study will have sufficient precision to provide 90% confidence interval on toxicity that will be no wider than 22%. For rare toxicities with 2% true probability, there will be 75% probability of observing one or more toxicities in either treatment arm. For rare toxicities with 3% true probability, there will be 85% probability of observing one or more toxicities on either treatment arm. Formal comparison of toxicity rates between the arms is not a goal of this trial and the sample size will provide sufficient power for detecting only relatively large differences in adverse events.

This study will include one interim analysis of PFS for efficacy at 20 months (10 months before the projected end of the accrual period, which should correspond to 57 failures under the alternative hypothesis or 50% information time). A log rank test using an O'Brien-Fleming boundary will be conducted and under the alternative hypothesis there is probability of 0.42 that the efficacy boundary will be crossed. Regarding futility, if at the interim analysis the estimated hazard ratio for experimental/control is ≥1 the study will be reported as negative. If the estimated hazard ratio is less than 1 but the efficacy boundary is not crossed, the study will have its final analysis at 42 months of study time or 12 months post end of accrual. Results of the interim analysis will be presented to the ECOG-ACRIN Data Safety Monitoring Committee (DSMC) when appropriate.

9.3 Feasibility

G3 gastroenteropancreatic neuroendocrine carcinomas are rare, accounting for approximately 11% of all neuroendocrine neoplasms. As such, a randomized trial in this patient population has never been conducted. Given the lack of data available and the rarity of this disease, the Neuroendocrine Task Force is committed to pursuit of a clinical trial in this patient population and this trial will be heavily promoted throughout the National Clinical Trials Network cooperative groups. As it is a rare disease, intergroup participation will be required to meet accrual goals. As there is no precedent providing an estimate of patients available for this trial, tumor registry and database data have been collected from

many members of the Neuroendocrine Task Force for a preliminary estimate of feasibility. As all cooperative group sites would be able to participate, we anticipate that a greater number of patients than listed below will be available for the study.

9.4 Safety monitoring

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

9.5 Study Monitoring

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

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9.6 Gender and Ethnicity (Revised for July 2019 amendment)

Based on previous data from ECOG ACRIN neuroendocine trials the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	2	2
Not Hispanic or Latino	34	44	78
Ethnic Category: Total of all subjects	**34**	**46**	**80**

Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	2	2
Black or African American	5	8	13
Native Hawaiian or other Pacific Islander	0	0	0
White	29	36	65
Racial Category: Total of all subjects	**34**	**46**	**80**

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.

9.7 Correlative Studies Statistics

9.7.1 Pathology samples will be collected from all eligible patients. Ki-67 will be determined using immunohistochemical analysis and will be reported as a percentage ranging from 0-100%, based on counting at least 500 tumor cells in the regions with the highest labeling rate ("hot spots")

The primary analysis of Ki-67 will be to evaluate the interaction, if any, between Ki-67 as a continuous measure and treatment. Cox regression of logistic regression, as appropriate, will be used to identify whether the treatment effect varies by Ki-67 for PFS, OS, and RR. Subsequent analyses to identify "optimal" cutpoints from continuous Ki-67 measurement are considered exploratory.

Receiver operating characteristics (ROC) analysis will also be performed to determine the optimal cutoff value in Ki-67 that defines patients with prolonged OS, where prolonged OS is defined as survival of at least 12 months. Hence in these analyses, survival will be considered as a binary endpoint. This optimal cutoff will serve for differentiating patients with features that are clinically more consistent with a well differentiated non-small cell gastrointestinal neuroendocrine tumor from the analysis set.

For the series of Ki-67 values observed in the data, Youden's index will be calculated and with the highest index we will identify the threshold that minimizes the false positive and false negative rates for best detecting prolonged OS. Optimal cutoff values of Ki-67 with respect to response to temozolomide and capecitabine will be determined in similar exploratory manner but the analysis will differ in that we will only include patients whose Ki-67 and response to temozolomide and capecitabine are available. Response to temozolomide and capecitabine is defined as complete response or partial response defined by RESIST 1.1 following initiation of therapy.

Concordance between Ki-67 measured centrally versus registering institutions' pathology assessments will also be investigated and reported. Intra-class correlation will be calculated to assess agreement amongst the two continuous measures.

We will also assess the prognostic significance of well differentiated versus poorly differentiated non-small cell gastroenteropancreatic neuroendocrine tumors in relationship to survival and response to treatment in a similar manner, via Cox proportional hazard models for time to event endpoint and logistic regression for objective response.

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Rev. Add3

10. Imaging Study Submissions

Baseline standard of care images including a CT of the chest, abdomen and pelvis will be obtained for each patient. If octreotide scan (SPECT or SPECT/CT) , ^{68}Ga-PET scans and ^{18}F-FDG PET scans are done, it is requested that images be submitted. Subsequent CT scans of the chest, abdomen and pelvis will be obtained every two months. Additional octreotide scans, ^{68}Ga-PET scans and ^{18}F-FDG PET scans may also be obtained per physician discretion. As the radiographic characteristics of G3 gastroenteropancreatic neuroendocrine carcinomas have not been extensively studied, building of a centralized bank of images will generate a resource upon which researchers may draw to ask further radiographic questions regarding this tumor type. This data set of serial images from approximately 80 patients with G3 gastroenteropancreatic neuroendocrine carcinomas will serve as one of the largest NEC image banks. 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, ^{68}Ga-PET scans, [^{18}F] FDG-PET, perfusion CT, octreotide scan or any combination) of the chest, abdomen and pelvis including all phases completed will be submitted to the ACR Imaging Core Laboratory per Section 10.2 instructions.

10.1.2 Standard practice imaging studies for the trial per EA2142 procedures include:

- Pre-treatment baseline scan for eligibility assessment.
- Imaging studies during study-prescribed treatment—(e.g. CT scans or MRIs at every 8 week intervals).

10.1.3 Three-phase contrast-enhanced CT acquisition as outlined below is recommended.

- Late arterial phase through the abdomen;
- Portal venous phase through the abdomen and pelvis;
- Delayed (equilibrium) phase through the abdomen at 3-4 minutes after contrast administration;
- If performed per standard institutional practice, optional perfusion CT sequences of an area of interest may be performed if available at the participating institution.

10.2 Images Submission

10.2.1 See Section 4.4.5 for instructions.

11. Specimen Submissions

Fixed paraffin-embedded tumor (mandatory) from core biopsy or surgery is to be submitted for central diagnostic review and, per patient consent, research studies. Peripheral blood (per patient consent) are also to be submitted for research.

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

LABELING: Specimens are to be labeled clearly with the ECOG-ACRIN protocol number "EA2142", patient initials, date and time of collection, and sample type. All sample submissions are to be accompanied with an STS shipping manifest.

SHIPPING ACCOUNT: Samples shipped to the ECOG-ACRIN CBPF are to be shipped using the CBPF's FedEx account using the FedEx On-Line Services. Access to the shipping account for specimen shipments to the ECOG-ACRIN CBPF at MD Anderson 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

11.1 Submissions to the Central Biorepository and Pathology Facility (CBPF)

The ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) is the receiving laboratory for all specimens submitted from patients participating in this trial.

11.1.1 Pathology Materials - MANDATORY

Submission of pathology materials from all patients is **mandatory**. The required materials are to be submitted within four (4) weeks following randomization. The submitting pathologist and clinical research associate should refer to Appendix I (Pathology Submission Guidelines) for guidelines and summary of submission requirements. Failure to submit the required materials may render the patient's data unevaluable.

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

A. FFPE TUMOR TISSUE

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

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

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

- Mandatory: Two (2) H&E slides.

- Mandatory: Minimum of five (5) unstained charged slides 4 or 5 µm thick.
- Additional materials from consenting patients: Two (2) 4mm cores, 15-25 unstained slides.

- All original stained diagnostic slides.

  NOTE: These slides will be returned to the site upon completion of the review which is retrospective and will be performed in batches. If the return of these slides is to be expedited, please indicate as such in the appropriate comment field in STS.

B. FORMS

- A copy of the surgical (if appropriate) and pathology reports
- Immunologic studies, if available
- Sample Tracking System Shipping Manifest

Ship Frozen or ambient →

11.1.2 Whole Blood, ACD vacutainer

Blood is to be collected and submitted from patients who answer "Yes" to "I agree to have my samples collected and I agree that my samples and related information may be used for the laboratory studies described above."

This specimen is to be collected after randomization, but prior to start of treatment

Draw one (1) 8-10mL ACD DNA vacutainers

Ship at ambient with the tissue the day of collection. OR, freeze at ≤ -70°C and ship on dry ice. If samples are frozen at -20°C ship on dry ice within 1 week of draw.

NOTE: Glass vacutainers cannot be frozen, so if glass vacutainers are used, transfer peripheral blood to cryovials for freezing.

11.2 Shipping Guidelines

The receiving laboratory is not available to receive shipments over holidays or weekends.

The required initial diagnostic tumor tissue materials, reports and forms are to be submitted within four (4) weeks following patient randomization. It is requested that the blood samples be submitted with or prior to submission of the tissue. If blood samples are frozen they must be shipped overnight on dry ice. Tissue and blood must be packaged in a manner that the tissue cannot freeze.

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

Shipping Address

ECOG-ACRIN 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

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

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.

Important: Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

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

Please direct your questions or comments pertaining to the STS to ecog-acrin.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. Include site contact information on the form. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory the day of shipping. Indicate the shipping tracking number and the appropriate Lab 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

Testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies. Tissue

specimens will be processed and distributed to investigators for the central diagnostic outlined in Section 11.

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

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

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

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

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.

12. Laboratory Research Studies

12.1 Central Diagnostic and Ki-67 Analysis (MANDATORY, INTEGRATED)

The pathologic diagnosis of G3 gastroenteropancreatic neuroendocrine carcinomas is difficult and diagnostic criteria can be variable between institutions. Therefore, a central pathology review will be conducted on tumor specimens of all patients participating in the study to confirm diagnosis. This will be a retrospective review to ensure that only patients meeting inclusion criteria are considered in the final statistical analysis. Any H&E slides made at the original institution of the patient will be requested along with other diagnostic slides including but not limited to Ki-67, chromogranin and synaptophysin. Pathology reports from the originating institution will also be obtained. Tissue samples will be assessed for tumor histology and mitotic index using standard H&E staining techniques. Ki-67 labeling rate will be evaluated using immunohistochemistry (see methods in Section 12.2.1 below). While institutional Ki-67 slides will be evaluated for comparison if available, all patients will have an unstained slide used for Ki-67 analysis. The Ki-67 will be determined by a manual count of at least 500-2000 cells performed on a printed photograph of the stained slide. In addition to manual scoring, computerized imaging analysis will also be conducted on each specimen.

Marker	Primary Ab	Dilution	Company	Secondary Ab	Dilution
Ki-67	Monoclonal	1:100	DAKO	a-mouse	1:200

We will also conduct subset analyses with respect to PFS, OS, and response rate to evaluate the prognostic significance of Ki-67 with regard to these clinical endpoints.

This diagnostic review will be performed under the direction of David Klimstra, MD at Memorial Sloan-Kettering Cancer Center.

12.2 Research Studies

The following correlative studies are proposed research studies. At the time it is determined that these studies will be performed, a full correlative science proposal or amended protocol document with formal statistical analysis plan for the marker studies will be submitted to and reviewed by CTEP.

12.2.1 MGMT IHC and Promoter Methylation

Immunohistochemistry: MGMT immunohistochemical evaluation will be performed using the Ventana Discovery XT platform. Ventana CC1 standard pretreatment solution will be used. A monoclonal antibody against MGMT (Invitrogen) will be applied then Omni Map Polymer for 16 minutes at a dilution of 1:150. A secondary anti-mouse antibody will be applied at a dilution of 1:200. Immunohistochemical expression of MGMT will be interpreted as “present” or “absent” where absent is classified as a complete absence of labeling in the face of positive staining in adjacent non-neoplastic cells, which serve as an internal positive control.

Marker	Primary Ab	Dilution	Company	Secondary Ab	Dilution
MGMT	Monoclonal	1:150	Invitrogen	a-mouse	1:150

MGMT Promoter Methylation: DNA will be extracted from formalin fixed paraffin embedded tissue using the DNeasy Tissue Kit (Qiagen, 69506) and concentration assessed using a Nanodrop assay. Bisulfite conversion of genomic DNA will be performed using the Zymo EZ-DNA Methylation-Direct Kit (Zymo Research, D5021), converting non-methylated cytosines to uracuils while methylated cytosines remain resistant to conversion. Bisulfite converted genomic DNA will be subjected to PCR amplications followed by pyrosequencing using the PryoMark Q24 instrument and methylation status will be determined using the PyroMark Q24 software.

12.2.2 Molecular Profiling of Poorly Differenctiated (G3) Gastroenteropancreatic Neuroendocrine Tumors (INTEGRATED)

Immunohistochemical staining will be performed on fixed paraffin embedded tumor tissue to evaluate the following reference gene set—DAXX, ATRX, CDK4, mdm2, SSTR2, Rb, p53, and MGMT. Molecular profiles will then be correlated with pathologic features, clinical outcome data and radiographic data.

Staining will be performed using the Ventana Discovery XT platform. The Ventana CC1 solution will be used for pretreatment followed by the Ventana DABMap Development Kit. The individual protocol may vary slightly depending on the antibody being evaluated. Primary antibodies (see table below) will be applied for 60 minutes at their respective dilutions. Secondary antibodies will be applied at a 1:200 dilution for 60 minutes. An a-mouse secondary antibody will be used for monoclonal primary antibodies and an a-rabbit secondary antibody will be used for polyclonal primary antibodies. Immunohistochemical expression of each antibody will be scored on a semi-quantitative scale that includes the percentage of cells labeling and the intensity (0, 1+, 2+, 3+); the criteria to determine ultimate positivity will vary depending on the antibody.

If availability issues in regard to slides available for studies become an issue, IHC studies to be conducted will be determined by the study team.

Marker	Primary Ab	Dilution	Company	Secondary Ab	Dilution
ATRX	Polyclonal	1:500	Sigma	a-rabbit	1:200
DAXX	Polyclonal	1:100	Sigma	a-rabbit	1:200
CDK4	Polyclonal	1:5000	Santa Cruz	a-rabbit	1:200
mdm2	Monoclonal	1:500	Calbiochem	a-mouse	1:200
SSTR2	Polyclonal	1:100	Abcam	a-rabbit	1:200
Rb	Monoclonal	1:50	LEICA	a-mouse	1:200
p53	Monoclonal	1:500	DAKO	a-mouse	1:200

12.3 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 ***EA2142*** 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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Randomized Phase II Study of Platinum and Etoposide versus Temozolomide and Capecitabine in Patients with Advanced G3 Non-Small Cell Gastroenteropancreatic Neuroendocrine Carcinomas

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 EA2142
4. ECOG-ACRIN Generic Specimen Submission Form (#2981)

Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG Pathology Coordinating Office:

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

NOTE: All submissions must be logged and tracked via the ECOG-ACRIN Sample Tracking System (STS). See Section 11.2

All submitted materials must be labeled with the protocol trial, the trial-specific patient case ID, patient initials. Sites accession numbers must be provided with the samples submitted.

Pre-trial Diagnostic Materials

1. Institutional pathology report, including immunological reports if available
2. STS-generated shipping manifest
3. Diagnostic tumor slides
4. Representative tumor tissue block (metastatic preferred, primary accepted)

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

   - Mandatory: one (1) H&E, five (5) unstained slides 4µm thick
   - Additional materials requested: 15-20 slides, two (2) 4mm cores.

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

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 Pathology Coordinating Office by telephone (312) 503-3385.

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

MEMORANDUM

TO: _____
(Submitting Pathologist)

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

DATE: _____

SUBJECT: Submission of Pathology Materials for EA2142: Randomized Phase II Study of Platinum and Etoposide versus Temozolomide and Capecitabine in Patients with Advanced G3 Non-Small Cell Gastroenteropancreatic Neuroendocrine Carcinomas

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 diagnostic review and research studies.

Return 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 Central Biorepository and Pathology Facility at MD Anderson.

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

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

Results of the diagnostic review will be distributed to you upon completion of the review. This review will be retrospective and will not impact patient participation in E2142.

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility at 844-744-2420 (713-745-4440 Local or International Sites) or email: 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

9/12/14

Randomized Phase II Study of Platinum and Etoposide versus Temozolomide and Capecitabine in Patients with Advanced G3 Non-Small Cell Gastroenteropancreatic Neuroendocrine Carcinomas

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 web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

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

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

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

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

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

Randomized Phase II Study of Platinum and Etoposide versus Temozolomide and Capecitabine in Patients with Advanced G3 Non-Small Cell Gastroenteropancreatic Neuroendocrine Carcinomas

Appendix III

Patient Pill Calendar

NOTE: This pill calendar is for patients randomized to Arm A **ONLY.**

Pill Calendar Directions

1. Take your scheduled dose of each pill.
2. If you forget, the missed pills will not be taken later.
3. "Cap"- is an abbreviation for "Capecitabine" and "Tem" is an abbreviation for "Temozolomide"
4. Please bring the bottle, any leftover pills, and your pill calendar to your next clinic visit.
5. Please list any other drugs you are taking at home such as OTC products, herbal medicines, tea, or other prescribed drugs.
6. When taking Capecitabine:
   - Take doses at least 12 hours (+/- 2 hours) apart.
   - Capecitabine pills should be swallowed with water within 30 minutes after a meal.
   - Capecitabine pills may NOT be crushed.
7. When taking Temozolomide:
   - Ondansetron should be taken to prevent nausea 30-60 minutes prior to the temozolomide dose.
   - Temozolomide should be taken at night by mouth after fasting from solid food for two hours.
   - Temozolomide pills must not be crushed and must be administered whole.
   - Do not repeat dose if vomiting occurs after dose is administered.

Patient Pill Calendar

This is a calendar on which you are to record the time and number of pills you take each day. You should take your scheduled dose of each pill. **Note the times and the number of pills that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused pills and your completed pill calendar to your doctor's visits.

Day	Date			Times pills taken				Number of pills taken				Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
	Month	Day	Year	AM		PM		AM		PM		
1				Cap:		Cap:		Cap:		Cap:		
2				Cap:		Cap:		Cap:		Cap:		
3				Cap:		Cap:		Cap:		Cap:		
4				Cap:		Cap:		Cap:		Cap:		
5				Cap:		Cap:		Cap:		Cap:		
6				Cap:		Cap:		Cap:		Cap:		
7				Cap:		Cap:		Cap:		Cap:		
8				Cap:		Cap:		Cap:		Cap:		
9				Cap:		Cap:		Cap:		Cap:		
10				Cap:		Cap: Tem:		Cap:		Cap: Tem:		
11				Cap:		Cap: Tem:		Cap:		Cap: Tem:		
12				Cap:		Cap: Tem:		Cap:		Cap: Tem:		
13				Cap:		Cap: Tem:		Cap:		Cap: Tem:		
14				Cap:		Cap: Tem:		Cap:		Cap: Tem:		
15-28												

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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.

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Appendix V

Patient Drug Information Handout and Wallet Card

Information for Patients, Their Caregivers, and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, Temozolomide/Capecitabine. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Capecitabine interacts with Coumadin resulting in an increased tendency for bleeding. Patients participating in this clinical trial are not permitted to receive Coumadin

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Temezolomide or capcitabine may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Coumadin may interact with one of your study drugs. Do not start taking this medication while you are receiving study treatment as part of this clinical trial.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is

  _____ and he or she can be contacted at

  _____

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **_____.** This clinical trial is sponsored by the NCI.

_____ may interact with drugs that are ***[processed by your liver, or use certain transport proteins in your body or affects the electrical activity of your heart]***. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

_____ interacts with a ***[specific liver enzyme called CYP_____, transport protein, heart's electrical activity (QTc prolongation]***, and must be used very carefully with other medicines that interact with ***[this enzyme, transporter, or agent]***.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered ***"[strong inducers/inhibitors or substrates of CYP_____, or transporter; or affect the heart's electrical activity.]***"
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is **_____** and can be contacted at **_____.**