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MC0845: A Phase 2 Trial of Temsirolimus and Bevacizumab in Patients with Endometrial, Ovarian, Hepatocellular Carcinoma, Carcinoid or Islet Cell Cancer

P2CAddendum 15 - *Pending*

Bolded text is newly added; ~~strikethrough~~ text has been deleted.

#	Section	Revision
1.	Throughout protocol	The headers of the document have been updated to the new NCI version date.
2.	Title Page	Henry Pitot, MD replaces Charles Erlichman, MD as PI; Dr Erlichman is listed as co-investigator.

3.	8.22, pages 61-66	An updated CAEPR for bevacizumab version 2.4 dated May 23, 2016 replaces the prior version 2.3 dated August 1, 2013. The revisions are as follow:
		
		• Added New Risk:
		  • Less Likely: Creatinine increased; Erythroderma
		  • Rare but Serious: Avascular necrosis; Gallbladder perforation
		
		• Increase in Risk Attribution:
		  • Changed to Less Likely from Also Reported on Bevacizumab Trials But With Insufficient Evidence for Attribution: Dry skin; Generalized muscle weakness; Hyperglycemia; Hypokalemia; Hyponatremia
		  • Changed to Rare but Serious from Also Reported on Bevacizumab Trials But With Insufficient Evidence for Attribution: Palmar-plantar erythrodysesthesia syndrome
		
		• Deleted Risk:
		  • Less Likely: Cardiac troponin I increased
		  • Also Reported on Bevacizumab Trials But With Insufficient Evidence for Attribution: Infections and infestations - Other (aseptic meningitis)
		
		• Provided Further Clarification
		  • Footnote # 7 has been altered to read, "Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation."
		  • Footnote #11 has been added and reads, "There have been reports of non-mandibular osteonecrosis (avascular necrosis) in patients under the age of 18 treated with bevacizumab."

Title: A Phase II Trial of Temsirolimus and Bevacizumab in Patients with Endometrial, Ovarian, Hepatocellular Carcinoma, Carcinoid or Islet Cell Cancer

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NCI-Supplied Agent:
Bevacizumab (NSC 704865, IND 7921)
Temsirolimus (NSC 683864, IND 61010)

IND Sponsor: DCTD, NCI.

Document History	Effective Date	Document History	Effective Date
Activation	September 8, 2009	Addendum 9	July 18, 2012
Addendum 1	February 22, 2010	Addendum 10	October 8, 2012
Addendum 2	June 8, 2010	Addendum 11	June 4, 2013
Addendum 3	August 23, 2010	Addendum 12	November 6, 2013
Addendum 4	February 8, 2011	Addendum 13	April 11, 2014
Addendum 5	June 21, 2011	Addendum 14	July 10, 2014
Addendum 6	June 21, 2011	Addendum 15	Pending
Addendum 7	December 22, 2011		
Addendum 8	March 6, 2012		

This trial is supported by the NCI Cancer Trials Support Unit (CTSU). Participation is restricted to NCI-supported Phase 2 Contract (N01) sites. All Phase 2 Contractors will participate through the CTSU mechanism as outlined below.

- All participating investigators and research staff must be registered members of the CTSU and have an active **CTEP IAM account** (https://eapps-ctep.nci.nih.gov/iam). To ensure timely communication between the clinical site and the CTSU, it is critical that a CTSU Site Administrator and Data Administrator be designated at each site and that their CTEP IAM contact information remains current. Instructions on obtaining a CTEP IAM account and registering with the **CTSU** are outlined in the Registration Procedures section of this protocol.

- The **study protocol and all related forms and documents** may be downloaded from the 8233 Web page located under the Phase 2 Consortia Trials section of the CTSU Members' side of the web-site. Protocol document access is confined to the investigators and associates at Phase 2 contract sites (main members and affiliates). Go to http://www.ctsu.org, sign on with your username and password on the left hand side, click on the Protocols tab, then click on "Phase 2 Consortia Trials" and select trial 8233.

- Send **site registration documents** to the CTSU Regulatory Office in Philadelphia as outlined in the Registration Procedures section of this protocol.

- **Patient enrollments** will be facilitated by the CTSU. Fax patient enrollment documents to the CTSU Patient Registration desk as outlined in the Registration Procedures section of this protocol.

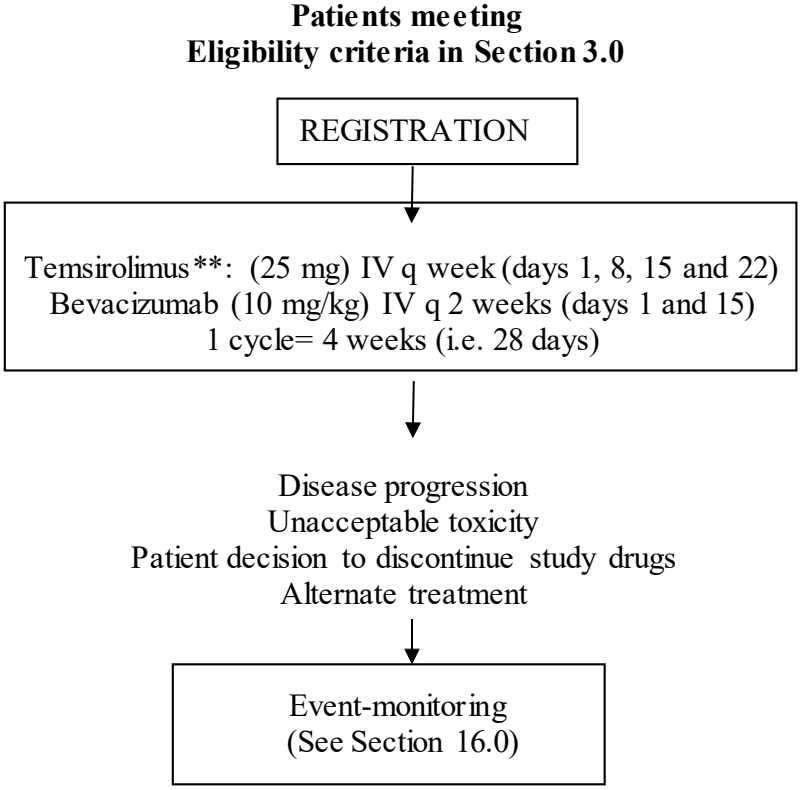
- **Data management activities** will be performed by CTSU Data Operations. This is a CTSU Remote Data Capture (RDC) study. All sites will submit CRF data electronically using the RDC system. Discrepancy management will be handled through the discrepancy management component of the RDC system. The RDC Production Application is for those individuals who have completed their training in the RDC system. Please go to the CTSU Members' side of the website (https://www.ctsu.org) and click on the "Clinical Data" tab at the top of your screen, followed by the "Remote Data Capture" link on the left-hand side of your screen. Select the "Training" tab to request a training account. Clinical reports should be submitted to CTSU Data Operations via fax. Details are outlined in the protocol section *Data Submission to Data Operations Center (CTSU)*.

Cancer Trials Support Unit (CTSU) Address and Contact Information

Mail or FAX site registration documents to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone - 1-866-651-CTSU (1-866-651-2878)
Fax – 215-569-0206

FAX patient enrollment forms to the CTSU Patient Registration desk as outlined in the Registration Procedures section of this protocol.
For answers to patient eligibility or treatment-related questions: Please contact: **Manisha H. Shah, MD (Carcinoid Tumor)** manisha.shah@osumc.edu **Timothy Hobday, M.D. (Islet Cell)** hobday.timothy@mayo.edu **Mark H. Einstein, M.D. (Endometrial Cancer)** meinstei@aecom.yu.edu **Robert Morgan, M.D. (Ovarian Cancer)** RMorgan@coh.org **Jennifer Knox, M.D. (Hepatocellular Carcinoma)** jennifer.knox@uhn.on.ca
All other questions (including forms-specific and remote data capture system questions) should be communicated by phone or e-mail to the CTSU Help Desk at: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative. CTSU Help Desk hours are 9:00 am – 5:30 pm. E.T. Mon-Fri (excluding holidays)
The CTSU Web-site is located at: Https://www.ctsu.org
NCI IDB contacts: Helen Chen, M.D. (bevacizumab) Helen_Chen@nih.gov L. Austin Doyle, M.D. (temsirolimus) doylela@mail.nih.gov

SCHEMA



Drug Names/Abbreviations

Generic name: temsirolimus P2C abbreviation: CCI-779	Generic name: bevacizumab P2C abbreviation: AVASTIN

**Omit in Bevacizumab-only cohort with Islet Cell Carcinoma.

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

1.11 To determine the response rate and progression-free survival at 6 months in patients with endometrial, ovarian, hepatocellular carcinoma, carcinoid or islet cell cancer.

1.12 To determine the toxicity of the combination of temsirolimus and bevacizumab in patients with endometrial, ovarian, hepatocellular carcinoma, carcinoid or islet cell cancer.

1.2 Secondary Objectives

1.21 To collect blood and tumor specimens from all patients entered on the trial for possible future analysis.

2. BACKGROUND

2.1 Redacted

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2.2 Temsirolimus (CCI-779, Torisel)

Temsirolimus (CCI-779, sirolimus 42-ester with 2,2-bis(hydroxymethyl) propionic-acid), an ester of the macrocyclic immunosuppressive agent sirolimus (rapamycin, Rapamune™), is a cytostatic cell cycle inhibitor with antitumor properties. The agent specifically inhibits the mammalian target of rapamycin (mTOR), a Ser/Thr kinase involved in the initiation of mRNA translation (reviewed in Dancey, 2002). Temsirolimus has been shown to inhibit the growth of a wide range of histologically diverse tumor cells, with the greatest sensitivity shown by cells derived from the central nervous system (CNS) cancers, leukemia (T-cell), breast cancer, prostate cancer, and melanoma [25]. Temsirolimus is being developed as a cytostatic agent to delay the time to tumor recurrence or progression or to increase survival in patients with various malignancies. Key features of this agent include its good tolerability, unique mechanism of action, ability to arrest cells in the G_1 phase, and ability to induce apoptosis. Intermittent schedules of temsirolimus administration have been evaluated in clinical studies because nonclinical data suggest such schedules minimize the agent's

immunosuppressive effects while maintaining antitumor activity.

Mechanism of Action

The observed antitumor and immunosuppressive properties of rapamycin analogs are due to their ability to disrupt the mTOR-dependent signaling pathway [26]. mTOR, a member of the phosphatidylinositide 3'-kinase (PI3K)-related family, is located predominantly in the nuclear fraction of both neoplastic and normal cells [27]. mTOR activation triggers resting cells to increase the translation of a subset of mRNAs whose proteins are required for cell cycle progression from G_1 to S phase. mTOR regulates essential signal transduction pathways and is involved in the coupling of growth stimuli with cell cycle progression. Experimental data indicate that mTOR acts downstream of the PI3K/Akt pathway and is phosphorylated in response to mitogenic signals [26]. Early studies reported that mTOR was dedicated to initiating mRNA translation in response to favorable nutrient environments [28]. In fact, cells treated with rapamycin undergo changes that are strikingly similar to those observed during conditions of starvation. These include mTOR inactivation, down regulation of translation, G_1 arrest, accumulation of glycogen stores and altered transcription patterns [28]. More recent studies have demonstrated that mTOR is involved in regulating many aspects of cell growth, including organization of the actin cytoskeleton, membrane traffic, protein degradation, protein kinase C (PKC) signaling, ribosome biogenesis, and transcription (reviewed in Schmelzle and Hall, 2000).

Temsirolimus reacts with the ubiquitous intracellular FK506-binding protein 12 (FKBP12), forming a temsirolimus/FKBP12 complex that is a potent inhibitor of the highly conserved kinase mTOR [29]; [30]. Inhibition of mTOR leads to suppression of several downstream signaling effectors, including the ribosomal subunit $p70^{S6k}$ and the eukaryotic initiation factor 4 binding protein 1 (4E-BP1) [31]. These two proteins play key roles in ribosomal biogenesis and cap-dependent translation, respectively [32]. The extent of phosphorylation of these two downstream proteins ($p70^{S6}$ kinase and 4E-BP1) may therefore serve as indicators of temsirolimus biologic activity *in vivo*. Inhibition of the synthesis of ribosomal proteins and elongation factors, required to accelerate the process of cell division, are thought to contribute to the anti-proliferative effects of rapamycin analogs [33]. While temsirolimus inhibits the translation of only a subset of mRNAs, inhibition of mTOR can lead to a substantial decrease (~15%) in overall protein synthesis [34].

Tumors that rely on paracrine or autocrine stimulation of receptors that constitutively stimulate the PI3K/Akt/mTOR pathway or tumors with mutations that activate the PI3K/Akt signal transduction pathway may depend on rapamycin-sensitive pathways for growth and therefore may be particularly sensitive to rapamycin analogs. The tumor suppressor gene PTEN is known to play a major role in embryonic development, cell migration, and apoptosis (reviewed in Yamada and Araki, 2001). PTEN acts as a lipid phosphatase that regulates major signal transduction pathways and effectively terminates PI3K-mediated signaling [35]. PTEN mutation is associated with constitutive activation of the PI3K/Akt pathway, resulting in tumors that are generally resistant to apoptosis. PTEN status in tumor cells may therefore be an important predictor of sensitivity to

rapamycin analogs [26]. Preliminary evidence suggests that breast cancer cell lines containing PTEN mutations are sensitive to growth inhibition by rapamycin [36]. Additional studies in PTEN-deficient human tumor cell lines and PTEN knockout mice have demonstrated sensitivity to growth inhibition by temsirolimus. Temsirolimus produced remarkable sensitivity to G_1 arrest (ID_{50} < 1nM) in PTEN-deficient myeloma cell lines, while myeloma cells containing wild type PTEN were at least 1000-fold less sensitive to the agent [37]. Also, studies of glioblastoma cell lines indicated that low PTEN protein expression was strongly linked with sensitivity to temsirolimus-mediated growth arrest [38]. Together, these studies indicate that the molecular identification of PTEN mutations or other mutations that lead to constitutive activation of the pathway within tumor cells might be predictive of sensitivity to temsirolimus therapy [39].

Summary of Clinical Studies

Temsirolimus safety, pharmacokinetics, and preliminary antitumor effects were evaluated in a phase 1 dose-escalation study with doses of 7.5-220 mg/m^2 given as a weekly intravenous (IV) infusion to 24 patients with advanced malignancies [40]. Although the maximum tolerated dose (MTD) was not reached, 220 mg/m^2 appeared to be the maximum acceptable dose, with thrombocytopenia being dose limiting with repeated dosing. No clinically relevant immunosuppressive effects were observed during treatment, although herpes simplex infections were observed in five patients. The most frequent drug-related adverse events were acneiform maculopapular rashes and mucositis/stomatitis (18 of 24 patients, 75%). Confirmed partial responses (PRs) were observed in 2 of 24 patients evaluated, one each with renal cell carcinoma (RCC) and breast cancer.

Data from *in vitro* studies of A498 human renal cell lines indicated that temsirolimus had a median growth inhibitory concentration (IC_{50}) of 5 ng/mL [25]. Predicted modeling of IC_{50} (humans receiving doses as low as 10 mg) suggests that whole blood concentrations would be above the range of 1 ng/mL throughout the entire 1-week dose interval and above 5 ng/mL for the majority of this time period. It is expected that mTOR inhibition would be attained with a 25 mg dose.

Clinical pharmacokinetic data are available in patients with cancer receiving temsirolimus both IV daily x 5 days every 2 weeks, once weekly schedules, and orally daily x 5 every 2 weeks. These data indicate that there is no appreciable drug accumulation between cycles and that distribution is extensive. With increasing dose, exposure (AUC) increases in a less than proportional fashion. The mean volume of distribution at steady state (V_{dss}) is large (57 L after 2 mg IV dose; 900 L following a 250 mg IV dose) and increases with dose. Exposure to the hydrolytic product sirolimus is substantial with mean values of approximately 1.5-2.3-fold greater than those seen with temsirolimus following IV administration. Clearance (CL) of temsirolimus from whole blood increases with increasing dose from approximately 5.2L/h after a 2 mg dose to 100L/h after a 250 mg dose. Intersubject variability in CL at a given dose was modest and ranged from 16-27%. The terminal half-life ($t_{1/2}$) following temsirolimus doses of 25 to 250 mg is approximately 15 hours.

Pharmacokinetic results from the initial phase 1 study showed that the AUC increased proportionally with doses up to 150 mg, but doses higher than 300 mg yielded high AUCs and low CL in some patients [40]. The mean Vd_{ss} was large with mean values of 127-384 L, while the temsirolimus mean terminal $t_{1/2}$ decreased from 22 hours (34 mg/m^2) to 13 hours (220 mg/m^2) as the dose increased. Similar pharmacokinetic data were reported for 16 patients following their initial dose of temsirolimus of 25, 75, or 250 mg delivered as a weekly 30-minute IV [41].

Phase II studies of single agent temsirolimus evaluating different doses of 25 mg, 75 mg, and/or 250 mg weekly IV have been undertaken in broad range of tumor histologies. The most promising activity has been seen in mantle cell lymphoma [42]; [43], other B-cell lymphomas [38] and endometrial carcinoma [44] with objective tumor response rates of 25-40%. Moderate activity has been reported in breast [45] and renal cell carcinoma [41]. Minimal to modest single agent activity has been seen in SCLC [46], melanoma [47] and GBM [48], [49] and multiple myeloma [50]. In general, lower doses appear to be as active as higher doses with better tolerability.

Recently, a phase 3 trial of temsirolimus, temsirolimus with interferon versus interferon in poor prognosis patients with RCC has been reported [51]. Of the 626 patients, overall survival of patients treated with temsirolimus was significantly prolonged compared to those treated with interferon (median 10.9 months versus 7.3 months, HR = 0.73, p = 0.0069). The combination of interferon and temsirolimus did not confer greater benefit than interferon alone, possibly due to compromised dose delivery of the agent(s).

Temsirolimus +Bevacizumab

It is clear that many of the new, targeted agents may not be of significant clinical benefit when used alone. Interfering with (multiple) pathways that affect the tumor cells and the tumor microvasculature may be a potentially promising strategy that can be of benefit for patients with renal cell cancer. Based on the mechanisms of action of both drugs, we hypothesize that the combination of temsirolimus and bevacizumab would induce stable disease in patients with progressive NET, ovarian cancer, HCC and endometrial cancer. Temsirolimus targets essential regulatory functions in the tumor cells as well as cells of the tumor stroma, and bevacizumab, by neutralizing VEGF, will target the tumor endothelium. Preclinical studies have suggested that the combination of the mTOR inhibitor rapamycin with a monoclonal antibody against VEGF is associated with enhanced antitumor effects in a pancreatic cancer model, compared to each agent alone [52]. The combination also was associated with a more potent *in vivo* antiangiogenic effect, as measured by tumor microvessel density, and enhanced apoptosis. This combination is at least additive, and may be synergistic (experiments to assess synergy were not possible in this *in vivo* model). This has led to a phase I/II trial of bevacizumab combined with temsirolimus in renal cancer which is being performed by the Mayo Clinic consortium. The trial reported at ASCO 2007 has demonstrated that the DLT was grade 3 hypertriglyceridemia. One patient also experienced a grade 3 mucositis. Other grade 3 adverse events that were not DLTs included hypertension, proteinuria, hemorrhage, nausea/vomiting, dehydration, anorexia, pneumonitis, anemia, and hypophosphatemia. The best responses in the 12 evaluable patients included 7 PRs and 3

SDs. This combination will be evaluated in both a company sponsored trial and by ECOG in first-line renal cancer. The RP2D from that trial is proposed for this multi-tumor phase 2 trial.

Endometrial Cancer

Endometrial cancer affects 40,000 women in the US each year and long-term outcomes in patients with advanced stage or recurrent disease is poor[53]. Endometrial cancer deaths are also rising, increasing over 100% during the past 20 years [54]. Approximately 40% of stage II/III tumors will recur and many of these will result in death. Investigations focusing on new approaches to improve outcomes in this patient population are warranted.

There have been several randomized controlled studies performed by the Gynecologic Oncology Group (GOG) and others addressing the issue of optimal therapy for patients with recurrent endometrial cancer. These studies have focused on three active agents identified in phase II trials: doxorubicin, platinum agents, and paclitaxel. Doxorubicin alone has been shown to have a 38% overall response rate with 26% of patients achieving a complete clinical response [55]. In GOG-107, 281 women were randomized to doxorubicin alone (60 mg/m2) vs. doxorubicin (60 mg/m2) plus cisplatin (50 mg/m2) (AP) which resulted in an improved response rate to combination therapy (25% vs. 42%, p=0.004) and PFS (3.8 vs. 5.7 months); however, there was no difference in overall survival (9 vs 9.2 months) [56]. It has been shown that Paclitaxel has significant single agent activity with a response rate of 36% in recurrent or advanced endometrial cancer [57]; however, in the randomized trial comparing paclitaxel with doxorubicin or the standard arm of AP, there was no difference in RR, PFS, or OS between the two arms [58]. In GOG 177, patients were randomized to AP versus TAP, which had significantly worse toxicity despite an improved ORR (57% vs. 34%; p<0.01), PFS (8.3 vs. 5.3 months; p<0.01) and OS (15.3 vs. 12.3 months; p=0.037) [59].

There is evidence that angiogenesis plays a significant role in endometrial cancer prognosis and disease progression [60]; [61]; [62]; [63]. Angiogenesis biomarkers correlate with endometrial cancer response to therapy and appear to have a prognostic role as well [64]. Bevacizumab has been shown to have overall clinical activity in previously treated patients with endometrial cancer. In a small study of 11 patients with recurrent endometrial cancer and leiomyosarcoma who had multiple sites of recurrence and have been treated with prior cytotoxic therapy, 2 had a PR and 3 had SD [65].

Temsirolimus and other mTOR inhibitors have shown single agent activity in patients who have recurrent or metastatic endometrial cancer [44]; [66]. In an NCIC trial of 27 patients with recurrent and metastatic endometrial cancer previously treated with hormones only who received single agent temsirolimus, a response rate of 25% and median progression free survival of 6 months were observed. [44]. Seven of 19 patients benefited from a different mTOR inhibitor AP25373 in a patient population who had progressed on chemotherapy. [66].

Due to the single agent activity of both temsirolimus and bevacizumab in endometrial

cancer patients who have been previously treated, this trial will combine these two agents to determine the efficacy of the combination as first line therapy.

Ovarian Cancer

Therapeutic targets including vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) have been shown to be important in the regulation of ovarian cancer. RAD001 (everolimus) [67] has been shown to play a central role in the regulation of ovarian cancer cell growth and cell cycle progression, to delay tumor onset and progression in a transgenic mouse model of ovarian cancer.[68]. Expression levels of Bcl-2 and CCND1/CDK4 may be predictive of the cellular effects of these agents in human ovarian carcinoma.[69]. VEGF expression in cell lines and murine models has been shown to be important in ovarian cancer cell growth and in stimulation of ascites production with increased production of VEGF leading to rapid ascites accumulation and inhibition of VEGF expression decreasing ascites production and cell growth. [70]. Furthermore, circulating levels of VEGF in mice has been shown to correlate with tumor response and response to therapy. [71] Administration of bevacizumab and rapamycin in combination in a mouse model of intraperitoneal cancer has been shown to inhibit of tumor growth more than either agent alone. [72]

While clinical activity of mTOR inhibitors have not yet been reported in human subjects with ovarian cancer, the activity of bevacizumab has been documented in phase II trials of the single agent alone and in combination with cytotoxic chemotherapy or other targeted agents. [73] treated forty-four patients with platinum-resistant ovarian cancer and reported a partial response in seven patients (15.9%). The median progression-free survival was 4.4 months and the median survival duration was 10.7 months. Bevacizumab-associated grade 3 or 4 adverse events included hypertension (9.1%), proteinuria (15.9%), bleeding (2.3%), and wound-healing complications (2.3%) and GI perforations (11.4%). The incidence of perforation was related to prior therapy as this complication was observed in 23.8% of patients receiving three prior chemotherapy regimens, compared with 0% of patients receiving two prior chemotherapy regimens ($P < .01$). It is also possible that heavily pretreated patients have a greater degree of tumor involvement, which may more directly contribute to the risk of perforation

The Gynecology Oncology Group reported a separate single agent trial of bevacizumab in persistent or recurrent ovarian cancer. [74]. Sixty-two patients having a median age of 57 years were treated. 66.1% received two prior regimens and 41.9% were considered platinum resistant. Two complete and eleven partial responses (21% ORR) were observed with a median response duration of 10 months. Twenty-five patients (40.3%) survived progression-free for at least 6 months. The median PFS and overall survival were 4.7 and 17 months, respectively. There was no significant association of prior platinum sensitivity, age, number of prior chemotherapeutic regimens, or performance status with the hazard of progression or death. Grade 3 adverse events included myelosuppression, gastrointestinal, hypertension, thromboembolism, allergy, hepatic, pain, coagulation, constitutional, and dyspnea. Grade 4 adverse events included one incident of pulmonary embolus, vomiting and constipation, and proteinuria.

Combinations of bevacizumab with metronomic cyclophosphamide and with erlotinib have also been reported. The California Cancer Consortium in collaboration with the Princess Margaret and Chicago Phase II Consortia [75] treated seventy patients with bevacizumab 10 mg/kg every two weeks with oral cyclophosphamide, 50 mg daily. The progression-free survival at 6 months was 56% with a median time to progression of 7.2 months. Partial responses were observed in 17 patients (24%). Grade 3 and 4 adverse events included hypertension, fatigue, and pain. Four episodes of gastrointestinal perforation or fistula were observed. In addition, two episodes each of CNS ischemia and pulmonary hypertension, and one episode each of gastrointestinal bleeding and wound healing complication were observed. There were three treatment-related deaths. Levels of VEGF, E-selectin, and thrombospondin-1 were not associated with clinical outcome. The Chicago Phase II Consortium in collaboration with the California Cancer Consortium and the Princess Margaret Consortium treated 13 patients with bevacizumab 15 mg/kg every three weeks with erlotinib 150 mg orally daily. [76] There were two major objective responses, one complete response of 16+ month duration and one partial response of 11 month (ORR 15%). Seven patients had a best response of stable disease. Grade 3 or 4 adverse events included anemia (1), nausea (2), vomiting (1), hypertension (1), and diarrhea (2). Two patients had fatal gastrointestinal perforations.

Based on this pre-clinical and clinical data suggesting additive or synergistic activity of these agents in epithelial ovarian cancer the efficacy of the combination of bevacizumab and temsirolimus in patients with persistent or recurrent ovarian cancer will be evaluated.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the 5th most common cancer worldwide with a rising incidence in the USA over the past three decades [77], [78], [79]. Worldwide, HCC is the third leading cause of cancer death after lung cancer and gastric cancer. The most common risk factors for development of HCC are chronic Hepatitis B or Hepatitis C infection and alcoholic cirrhosis. Many patients will have poor underlying liver function as a result of these co-morbidities [80].

The prognosis of HCC is poor. At presentation the majority of patients (70-85%) already have unresectable disease. Patients who present with localized disease (solitary nodule <5cm or up to 3 nodules <3cm each) may be eligible for surgical resection, transplantation or loco regional therapy such as chemoembolization or radiofrequency ablation (RFA) [81]. However, for those who do receive potentially curative surgery, recurrence rates are up to 50% within 2 years. For these patients who do relapse or progress, and for those patients who present with advanced disease, the prognosis is poor with survival measured in months. Poor underlying liver function in many patients, and the lack of effective systemic therapies are the main factors leading to poor survival in these patients [79, 82]. In advanced disease, systemic chemotherapy has not been shown to prolong survival. A 1997 meta-analysis of 27 chemotherapy trials concluded that non-surgical therapies were either ineffective or minimally effective [83].

Expectations for advancement in drug therapy for HCC patients lie with targeted agents. It is well recognized that many mutations and aberrant cell pathways drive primary liver

tumorigenesis. Even when comparing HCCs with similar etiologies there is tremendous molecular heterogeneity, suggesting that therapeutic advancements may require simultaneous targeting of more than one molecular pathway [84]. Targeting VEGF and mTOR pathways are 2 of the most promising strategies currently in HCC drug development.

VEGF is over-expressed in HCC, and the level of expression correlates with tumor grade. [85], and reviewed in [84]. Targeting angiogenesis is therefore an attractive approach in treating HCC, and anti-angiogenesis drugs such as sorafenib or bevacizumab have already demonstrated activity.

Sorafenib is a multikinase inhibitor with anti-angiogenic, pro-apoptotic and Raf kinase inhibitory activity. Following a phase II trial suggesting efficacy of sorafenib in HCC [86], a phase III randomized, placebo controlled trial in patients with advanced HCC with preserved liver function (Child-Pugh A) was performed. Treatment with sorafenib was associated with a statistically significant improvement in overall survival (10.7 versus 7.9 months, Hazard Ratio for death 0.69, 95% confidence interval [CI] 0.55-0.87, $p<0.001$), time to radiologic progression (5.5 versus 2.8 months, $p<0.001$) and disease control rate (43% versus 32%, p-0.002).[87]. In both the phase II and phase III studies, partial responses were uncommon (<5%) and no complete responses were observed. Therefore it appears that sorafenib works primarily as a cytostatic agent. In a subsequent Asian-Pacific phase III trial presented by Leung et al at ASCO 2008, sorafenib also impacted significantly survival in these very advanced HCC patients. These trials established sorafenib as a new reference standard of care in advanced HCC and serve to help validate the targeted agent approach in this disease. However given the absolute benefit for HCC patients is quite modest, further drug development is needed.

Bevacizumab has shown promising activity in a single arm phase II trial (NCI protocol number 5611) in advanced HCC patients [88]. The study included 46 patients, of whom 6 had objective responses (13%, 95% CI: 3-23%), and 65% were progression-free at 6 months. Median PFS was 6.9 months (95% CI: 6.5-9.1 months); overall survival was 53% at 1 year, 28% at 2 years, and 23% at 3 years. Grade 3-4 adverse events included hypertension (15%), thrombosis (6%, including 4% arterial thrombosis); Grade 3 or higher hemorrhage occurred in 11% of patients, including one fatal variceal bleed, although more rigorous screening for risk of bleeding appeared to reduce the incidence of these complications. Bevacizumab was associated with significant reductions in tumor enhancement by DCE MRI, and reductions in circulating VEGF-A and SDF-1 levels. The response rate of 13% in HCC with single agent bevacizumab suggests it is one of the more active agents studied to date in HCC and as good or better than seen in many other solid tumors where the drug has proven benefit.

The study of drugs that target mTOR are still preliminary in HCC but single agent phase I/II trials are underway. Studies in HCC animal models suggest mTOR is a promising therapeutic target in HCC [89], [90]. These models also suggest additive tumor control with dual m-TOR and VEGF targeting. The recognized toxicity profile of temsirolimus at the dose and schedule used in this study is likely to be quite manageable in an HCC population with preserved liver function (Child-Pugh A) and good PS.

As mTOR inhibitors have pre-clinical evidence in HCC and VEGF inhibitors have proven benefit, there is a good foundation to combine these 2 drug classes to study potential additive or synergistic benefit to patients with HCC. In addition there is a strong scientific rationale that combining bevacizumab with temsirolimus will maximize pathway inhibition by concurrently targeting parallel signaling mechanisms. Based on the current safety data that temsirolimus can be safely combined with bevacizumab this combination is very attractive to take forward in HCC patients.

Islet Cell Carcinoma

Metastatic Islet cell carcinoma (ICC) has few effective and tolerable therapies. Although potentially responsive to chemotherapy, response rates are generally in the range of 30-40% with systemic chemotherapy. Interferon is a toxic and minimally effective therapy.

These tumors are very vascular clinically. Expression of VEGF and its receptors has been demonstrated in tumor tissue. Multi-center phase II trials of the receptor TKIs sunitinib and sorafenib have demonstrated anti-tumor efficacy in islet cell carcinoma. These agents are felt to work predominantly through an anti-angiogenic mechanism. Sunitinib demonstrated a 17% response rate and sorafenib resulted in an 11% partial response rate, with an additional 14% having a minor response (20-29% reduction in tumor size by RECIST). In addition, bevacizumab has demonstrated anti-tumor activity in closely related carcinoid tumors, and is currently undergoing evaluation in a randomized phase III trial along with Sandostatin versus interferon and Sandostatin. However bevacizumab has not been evaluated as a single agent in islet cell tumors.

There is also evidence for a role for the mTOR pathway in ICC. Patients with tuberous sclerosis who have a mutation in the TSC2 gene which regulates mTOR tend to develop ICC. Increased IGF-1 expression is common in ICC and this may stimulate the mTOR pathway as well. A phase 2 trial of oral everolimus was reported with a 27% response rate, and there is a randomized phase III trial of everolimus vs best supportive care for ICC ongoing. A multi-center trial of temsirolimus was conducted in metastatic neuroendocrine tumors. A multi-center trial of CCI-779 was conducted in metastatic neuroendocrine tumors. Although a response rate of only 7% was observed, many patients had some tumor regression short of a PR, some with clinical improvement in symptoms, and an impressive median time-to progression of 10.6 months was demonstrated.

Given the experience of efficacy and tolerability for both anti-angiogenic and anti-mTOR therapy in ICC, this combination warrants evaluation in islet cell cancer.

Addendum:

Rationale for additional cohort of patients to be treated with bevacizumab alone:

Phase III trials of sunitinib and everolimus compared to placebo have now been completed and published. Both trials enrolled patients with progressive disease within

the previous 12 months and demonstrated clinically and statistically significant improvements in PFS compared to placebo. Both agents have been approved by the US FDA and become standard therapy for pancreatic NET (islet cell carcinoma).

However, in these trials, where the population could have a longer time than in our study to show disease progression (and thus potentially more indolent disease) and were candidates for placebo, the objective response rates were low; 5% for everolimus and 9% for sunitinib. Patients in both trials would not have received prior VEGF TKI pathway or mTOR inhibitors. (refs: Yao et al NEJM 2/10/2011; 514-23; Raymond et al NEJM 2/10/2011; 501-13).

In the protocol specified interim analysis of the first 25 patients with ICC on this trial (MC0845), a confirmed response rate of 52% was documented. This is very promising activity in this disease, and suggests clinical synergy of this regimen, as compared with either single class of agent alone. There are no good data at this time regarding the single agent activity of bevacizumab in ICC, and this may be important to interpreting the results of the current combination trial as well as CALGB 80701 (see below).

CALGB 80701 is an open intergroup trial that evaluates further the combined mTOR/VEGF pathway. This trial is a randomized phase II trial of either everolimus or everolimus combined with bevacizumab in patients with progressive metastatic ICC. Prior VEGFR TKI is allowed, but not mandated in this trial. Patients with prior mTOR inhibitor are excluded. This trial may provide further information regarding the activity of the combined targeted agents. If there are sufficient patients enrolled with prior anti VEGFR therapy, it may also provide some information regarding the activity in these previously treated patients.

Given the efficacy and safety data of the combination in this trial to date, we propose to add an additional cohort of patients to explore the activity of single-agent bevacizumab in ICC. This may provide information that informs future trial design in ICC in addition to that from our current trial and CALGB 80701. These patients will be treatment naïve for both mTOR inhibitor and VEGFR TKI.

Addendum: Due to the widespread use of everolimus and sunitinib as first line therapy for these patients, enrollment of treatment naïve patients has proven difficult. We will expand the eligibility to include patients with prior mTOR inhibitor use, but not Anti-VEGFR TKI which will reflect the practice patterns currently in place.

Carcinoid Tumors

Hypervascularity of the tumors is the hallmark characteristic of carcinoid tumors and VEGF is found to be a critical pro-angiogenic factor in carcinoid tumors. Using immunohistochemistry, strong, weak, and negative VEGF expression was observed in 32%, 54%, and 14% respectively among 50 cases of human gastrointestinal neuroendocrine tumors [27]. Furthermore, VEGF expression in this study was associated with poor progression free survival (P = .02). In the pre-clinical studies, bevacizumab

did not inhibit the growth of human carcinoid cells *in vitro* but significantly reduced tumor angiogenesis and impaired tumor growth in animal model of carcinoids. Based on this rationale for targeting angiogenesis in carcinoid tumors, a phase II clinical trial using bevacizumab was conducted in patients with carcinoid tumors and showed promising antitumor activity [91]. Forty-four patients on stable doses of octreotide were randomly assigned to 18 weeks of treatment with bevacizumab or PEG interferon alpha-2b. At disease progression (PD) or at the end of 18 weeks (whichever occurred earlier), patients received bevacizumab plus PEG interferon until progression. Bevacizumab in this trial was administered at dose of 15 mg/kg IV every 3 weeks in combination with standard dose of long acting octreotide. Among 22 patients enrolled in the "bevacizumab first" arm, 18% partial response and 77% stable disease was noted with 18-week progression free survival of 95% during the bevacizumab alone phase. In addition to clinical activity, 49% and 28% decrease in tumor blood flow assessed by functional CTs at day 2 and week 18 was noted in these patients. Common grade 3-4 AEs included hypertension (36%), fatigue (18%), headache (5%) and vomiting (5%).

In a phase II study of temsirolimus in 37 patients with advanced progressive neuroendocrine carcinoma (NEC), 21 patients with carcinoid tumors received intravenous weekly doses of 25 mg of temsirolimus [92]. Partial response rate of 5%, median time to progression of 6 months and 6-month progression free survival rate of 45% were noted in carcinoid tumor patients. The most frequent drug-related AE of all grades included: fatigue (78%), hyperglycemia (69%) and rash/desquamation (64%). Pharmacodynamic analysis revealed effective mTOR pathway down regulation.

Based on the safety and moderate anti-tumor activity of single agent bevacizumab and temsirolimus in patients with carcinoid tumor, activity of combination therapy in patients with metastatic carcinoid tumors will be evaluated.

3. PATIENT SELECTION

3.1 Inclusion Criteria - All Patients

3.11 Histologically or cytologically confirmed endometrial (endometrioid, uterine papillary serous carcinoma, and carcinosarcoma), ovarian (primary peritoneal/fallopian tube, serous, endometrioid, mixed, and poorly differentiated epithelial ovarian cancers (for purposes of eligibility, carcinosarcoma is considered a poorly differentiated carcinoma)), hepatocellular carcinoma , carcinoid or islet cell (neuroendocrine: well- or moderately-differentiated neuroendocrine) cancer which are locally advanced, recurrent or metastatic.(see HCC criteria for histology and or clinical diagnosis section 3.31).

3.12 ≥18 years of age.

3.13 Patients must have measurable disease as defined in Section 11.0. Patients having only lesions measuring ≥1 cm to <2 cm must use spiral CT imaging for both pre- and post-treatment tumor assessments. Patients who have had prior palliative radiotherapy to metastatic lesion(s) must have at least one measurable lesion(s) that have not been previously irradiated.

3.14 Radiation therapy (adjuvant or palliative) must be completed ≥4 weeks prior to registration, if applicable.

3.15 Required laboratory values obtained ≤ 7 days prior to registration:

• Absolute Neutrophil Count (ANC)	≥ 1500/mm^3
• Platelets	≥ 75,000/ mm^3
• Hemoglobin	≥ 9.0 g/dL
• Total bilirubin	≤ 1.5 x upper limit of normal (ULN) Note: total bilirubin and INR for HCC patients allowed as per Child-Turcotte-Pugh scoring see section 3.32 and appendix C
• Alkaline phosphatase	≤ 2.5 x ULN (≤ 5 x ULN if liver metastasis is present or patient is in HCC cohort)
• SGOT(AST)	≤ 2.5 x ULN (≤ 5 x ULN if liver metastasis is present or patient is in HCC cohort)
• Creatinine	≤ 1.5 x ULN
• Urinalysis	< 2+ protein*
• Fasting serum cholesterol	≤ 350mg/dL (≤ 9.0 mmol/L)
• Triglycerides	≤ 1.5 x ULN (mg/dL or mmol/L)**
• International Normalized Ratio (INR)	≤ 1.5 (unless the patient is on full dose warfarin see section 3.19a)

***Urine protein should be screened by dipstick or urine analysis. For proteinuria ≥2+, 24-hour urine protein should be obtained and the level should be < 2 g for patient enrollment.**
****Patients with Triglyceride levels > 1.5 x ULN can be started on lipid lowering agents and reevaluated within 1 week. If levels go to≤ 1.5 x ULN, they can be considered for the trial and continue the lipid lowering agents.**

NOTE: Cholesterol and triglyceride measurement and management are not required for single-agent bevacizumab cohort with Islet Cell carcinoma

3.16 ECOG Performance Status (PS) 0-1 (Appendix A).
Capable of understanding the investigational nature, potential risks and benefits of the study and able to provide valid informed consent.

3.17 Negative serum pregnancy test done ≤7 days prior to registration, for women of childbearing potential only. *NOTE: Patients and their partners should be practicing an effective form of contraception during the study and for at least 3 months following the last dose of this combined therapy.*

3.18 Full-dose anticoagulants, if a patient is receiving full-dose anticoagulants (except carcinoid tumors – see section 3.91), the following criteria should be met for enrollment: the subject must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin or on stable dose of LMW heparin.

3. 19a Prior systemic treatments for metastatic disease are permitted, including targeted therapies, biologic response modifiers, chemotherapy, hormonal therapy, or investigational therapy.

Exception: In the case of endometrial cancer no prior chemotherapy for metastatic or recurrent disease is allowed. Prior planned adjuvant chemotherapy is allowed.

3.19 b Patients who have had prior anthracycline must have a normal ejection fraction on LVEF assessment by MUGA or Echo ≤ 4 weeks prior to registration.

3.19c Availability of tissue **if applicable** (from the primary tumor or metastases) for tumor studies for banking.
Note: In the case of hepatocellular cancer if diagnosed by clinical and radiologic criteria only, availability of tissue not applicable.

3.19d Willingness to donate blood for **biomarker studies related to the type of therapies used in this trial and the tumor types being treated**.

3.2 Inclusion Criteria – Endometrial Cancer

Note: This group is permanently closed to enrollment

3.21 Any hormonal therapy directed at the malignant tumor is allowed. NOTE: Therapy must be discontinued at least one week prior to registration.

3.22 Prior systemic therapy including biologic and immunologic agents as adjuvant treatment must be discontinued at least 3 weeks prior to registration.

3.23 Recurrent or persistent endometrial adenocarcinoma, uterine papillary serous carcinoma and carcinosarcoma which is refractory to curative therapy or established treatments. NOTE: Histologic or cytologic confirmation of original primary tumor is required.

3.3 Inclusion Criteria – Hepatocellular Cancer

Note: This group is permanently closed to enrollment

3.31 HCC confirmed by biopsy OR diagnosed by clinical and radiologic criteria. All of the following criteria must be met or a biopsy is required:

- Known cirrhosis or chronic HBV or HCV infection,
- Hypervascular liver masses >2 cm, and either serum AFP > 400 ng/ml, or
- AFP >three times normal and doubling in value in the antecedent 3 months.

3.32 Child-Pugh A (≤6 points) or better liver status (see appendix C for calculating score).

3.33 Prior regional treatments for liver metastasis are permitted including:

- selective internal radiation therapy such as brachytherapy, cyberknife, radiolabelled microsphere embolization, etc.
- hepatic artery chemoembolization
- hepatic artery embolization
- hepatic artery infusional chemotherapy
- radiofrequency ablation.

NOTE: Patients must be ≥ 4 weeks from treatment and show progressive disease in the liver after regional therapy or must have measurable disease outside the liver.

3.34 Concomitant anti-viral therapy is allowed.

3.35 History of prior varices or evidence of varices on pre-study CT/MRI imaging is required to undergo endoscopy ≤ 4 weeks prior to registration.

Those who had received specific therapy (banding and/or sclerotherapy) and had not bled within the prior 6 months are eligible.

3.36 Suitably recovered from prior localized therapy, in the opinion of the investigator.

3.4 Inclusion Criteria - Islet Cell Cancer and Carcinoid Tumor
Note: The Carcinoid group is permanently closed to enrollment

3.41 Patient has evidence of progressive disease as documented by RECIST ≤7 months prior to study entry.

3.41.1 Carcinoid tumor cohort: Prior and concurrent long-acting somatostatin analogue therapy is required. Patient has to be on a stable dose of a long-acting somatostatin analogue ≥ 2 months prior to study entry with documentation of progressive disease on current dose.

3.41.2 Islet cell tumor cohort: Prior and/or concurrent long-acting somatostatin analogue therapy is allowed, but not required. If patient is continued on a long-acting somatostatin analogue, a stable dose for ≥ 2 months prior to study entry is required with documentation of progressive disease on current dose.

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3.42 Prior therapies allowed include:
- ≤2 prior cytotoxic chemotherapy regimens.
- Prior interferon ≥4 weeks prior to registration
- Radiolabelled octreotide therapy (Patients with prior radiolabelled octreotide therapy should have progressive disease after such therapy)
- Other investigational therapy.

NOTE: Islet Cell Single Agent Bevacizumab Cohort: Prior mTOR inhibitor is allowed

3.43 Prior regional treatments for liver metastasis are permitted including:
- selective internal radiation therapy such as brachytherapy, cyber knife, radiolabelled microsphere embolization, etc.
- hepatic artery chemoembolization
- hepatic artery embolization
- hepatic artery infusional chemotherapy
- Radiofrequency ablation.

NOTE: Patients must be ≥ 12 weeks from treatment and show progressive disease in the liver after regional therapy or must have measurable disease outside the liver.

3.5 Exclusion Criteria - All Patients

3.51 Prior therapy with VEGFR targeting agents or mTOR inhibitors (except as in HCC-see section 3.76 and in the Islet cell single agent bevacizumab alone cohort where prior mTOR inhibitor is allowed). **NOTE**: Prior use of bevacizumab is not allowed in any cohort.

3.52 Invasive procedures defined as follows:

- Major surgical procedure, open biopsy or significant traumatic injury ≤ 4 weeks prior to registration.
- Anticipation of need for major surgical procedures during the course of the study.
- Core biopsy ≤ 7 days prior to registration.

3.53 Serious or non-healing wound, ulcer or bone fracture.

3.54 History of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess ≤ 180 days prior to first date of bevacizumab therapy.

3.55 Evidence of bleeding diathesis or coagulopathy in the absence of therapeutic anticoagulation.

3.56 Evidence of a history bleeding ≤ 6 months such as hemoptysis, or cerebrovascular accident ≤ previous 6 months, or peripheral vascular disease with claudication on < 1 block, or history of clinically significant bleeding, because of the potential bleeding and/or clotting risk with bevacizumab.

3.57 Untreated central nervous system (CNS) metastases. Exceptions: Patients with known CNS metastases can be enrolled if the brain metastases have been adequately treated and there is no evidence of progression or hemorrhage after treatment as ascertained by clinical examination and brain imaging (MRI or CT) ≤ 12 weeks prior to registration and no ongoing requirement for steroids,.

- Anticonvulsants (stable dose) are allowed.
- Patients who had surgical resection of CNS metastases or brain biopsy ≤ 3 months prior to registration will be excluded.

3.58 Significant cardiovascular disease defined as congestive heart failure (New York Heart Association Class II, III or IV), angina pectoris requiring nitrate therapy, or recent myocardial infarction (≤ 6 months prior to registration) (Appendix F).

3.59 a Uncontrolled hypertension (defined as a blood pressure of ≥150 mmHg systolic and/or ≥ 90 mmHg diastolic).

3.59b Patient is on ACE inhibitors (benazapril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril). (Patients may have an alternate antihypertensive substituted).

NOTE: ACE Inhibitors are allowed in single agent bevacizumab cohort

3.59c Currently active, second malignancy other than non-melanoma skin cancers. *NOTE: Patients are not considered to have a 'currently active' malignancy if they have completed anti-cancer therapy and are considered by their physician to be at less than 30% risk of relapse.*

3.59 d Any of the following, as this regimen may be harmful to a developing fetus or nursing child:

- Pregnant women
- Breastfeeding women
- Men or women of childbearing potential or their sexual partners who are unwilling to employ adequate contraception (diaphragm, birth control pills, injections, intrauterine device [IUD], surgical sterilization, subcutaneous implants, or abstinence, etc.)

NOTE: The effects of the agent(s) on the developing human fetus at the recommended therapeutic dose are unknown.

3.59e Known hypersensitivity to other recombinant human antibodies or Chinese hamster ovary cell products.

3.59f Other uncontrolled serious medical or psychiatric condition (e.g. cardiac arrhythmias, diabetes, etc.).

3.59g Current therapy with a CYP3A4 inhibitor or inducer (See Appendix D for list of inhibitors and inducers). **NOTE: These agents are allowed in the single-agent bevacizumab Islet cell carcinoma cohort.**

3.59h Active infection requiring antibiotics.

3.59i Active bleeding or pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels, known varices).

3.59j Known HIV-positive.

3.6 Exclusion Criteria – Endometrial Cancer
Note: This group is permanently closed to enrollment

3.61 Received prior radiotherapy to any portion of the abdominal cavity or pelvis OTHER THAN for the treatment of endometrial cancer.

3.62 Any chemotherapy for metastatic or recurrent cancer.

3.63 Radiation therapy to > 25% of marrow bearing areas (Appendix E).

3.7 Exclusion Criteria - Hepatocellular Cancer
Note: This group is permanently closed to enrollment

3.71 Child-Pugh B or C classification (Appendix C).

3.72 Grade $\geq$ 3 hemorrhage $\leq$ 4 weeks prior to registration.

3.73 Prior liver transplant with evidence of recurrent or metastatic disease.

3.74 Patients on an active liver transplant list and considered likely to receive a liver transplant $\leq$ 6 months following registration.

3.75 Clinical evidence of encephalopathy.

3.76 Prior treatment with sorafenib or other VEGF inhibitors.
NOTE: Exceptions allowed for patients unable to tolerate the agent. Intolerance is defined in this protocol as a discontinued agent due to side effects with an exposure < to 4 weeks of drug, at any dose level.

3.8 Exclusion Criteria - Ovarian Cancer
Note: This group is permanently closed to enrollment

3.81 Clinical signs and symptoms of GI obstruction and require parental hydration/nutrition or tube feeding.

3.82 Evidence of free abdominal air not explained by paracentesis or recent surgical procedures.

3.83 Received more than two prior cytotoxic chemotherapy regimens for persistent or recurrent disease.

3.9 Exclusion Criteria – Carcinoid Cancer
Note: This group is permanently closed to enrollment

3.91 Patients on anticoagulant therapy.

4.0 REGISTRATION PROCEDURES

4.1 Investigator / Research Associate Registration

4.11 Obtaining a CTEP-IAM account

All participating investigators and research staff must be registered members of the CTSU. Access to the CTSU members' web site is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system. To register:

- Go to the CTSU web-site at https://www.ctsu.org and click on the Register tab on the upper right of your screen and follow links to the CTEP-IAM application, OR, go directly to https://eapps-ctep.nci.nih.gov/iam/ and click on the "New Registration" link on the left hand side of your screen and click on "Request New Account".
- Complete CTEP-IAM application instructions
- You will receive an email from the CTSU providing the status of your application within 2 to 3 business days. Once you receive your email from the CTSU, you may use your new CTEP-IAM username and password to access the CTSU Members side of the web site.

4.12 (Investigators Only) Obtaining an NCI Investigator number

Before the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV [signed and dated], Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web-site (logon to https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

4.2 Site Registration

4.21 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit all regulatory documents to the CTSU Regulatory Office in Philadelphia before patient enrollments may commence.

4.22 Downloading Regulatory Documents for 8233

Site registration forms can be downloaded from the 8233 Web page located under the Phase 2 Contractors section of the CTSU Members' side of the web site.

- Go to https://www.ctsu.org
- Sign in on the left hand side with the CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the Phase 2 Consortia link
- Select trial #8233
- Click on the Site Registration Documents link
- Download and complete the following forms:
    - CTSU IRB/Regulatory Transmittal
    - CTSU IRB Certification Form
- Mail or FAX completed forms to the CTSU Regulatory Office in Philadelphia along with a copy of your IRB Approved Model Consent (stamped, or signed and dated)

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone - 1-866-651-2878
FAX – 215-569-0206

4.23 Checking Your Site's Registration Status

Check the status of your registration packets by querying the RSS site registration status page of the CTSU Members' side of the web site.

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

Note: If possible, please allow three working days for site registration approval before attempting to enroll your first patient.

4.24 Order Blood Specimen Collection Kits

Order collection kits for blood draws **at least 2 weeks prior** to enrolling a patient. To request a kit, download the MML Fax Supply Order Form posted under the Site Registration Documents section of the 8233 Web page and fax as directed on the form. The form can also be found in the Forms Packet. See section 9.1 for details on blood sample collection and shipment.

4.3 Patient Registration

4.31 Contact the CTSU Patient Registration Office at 1-888-462-3009 and leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. Registration hours are between 9:00 a.m. and 5:00 p.m. Eastern Time, Mon-Fri. Registrations received after 5:00 p.m. Eastern Time will be handled the next business day. For immediate registration needs (e.g. enrollments that must be completed within approximately one hour or other extenuating circumstances) call the registrar cell phone at 1-301-704-2376.

4.32 Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- Eligibility Checklist

4.33 Fax these forms to the CTSU Patient Registrar at 1-888-691-8039. Registration desk hours are between 9:00 a.m. and 5:00 p.m. Eastern Time, Mon-Fri. Registrations received after 5:00 p.m. Eastern Time will be handled the next business day.

4.34 The CTSU Patient Registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and will follow-up with the site to resolve any discrepancies.

4.35 Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU Patient Registrar will forward patient enrollment documents to the Mayo P2C Registration Office to verify patient eligibility and perform the enrollment. The CTSU will convey the Mayo-assigned patient ID to the enrolling site followed by a confirmation of registration e-mail or fax.

4.36 Treatment on this protocol must commence at a N01 contract holder institution under the supervision of a physician investigator registered with NCI Pharmaceutical Management Branch (PMB) and CTSU.

4.37 Treatment cannot begin prior to registration and must begin within ≤7 days after registration.

4.38 Pretreatment tests/procedures must be completed within the guidelines specified on the test schedule.

4.39 a All required baseline symptoms (see Section 7.4) must be documented and graded.

4.39 b At the time of registration/randomization, the following will be recorded:

- **Patient has/has not given permission to keep tissue for future research to learn about, prevent, or treat cancer.**
- **Patient has/has not given permission to keep tissue for future research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).**
- **Patient has/has not given permission for tissue and blood to be used for genetic research (about diseases that are passed on in families) in the future.**
- **Patient has/has not given permission to be contacted in the future to take part in more research.**

5. TREATMENT PLAN

5.1 Study Drug Administration

5.1a Study Drug Administration

Agent	Dose	Route	Day	ReRx
TEMSIROLIMUS	25 mg IV q week	IV*	1,8,15,22	Q 28 days (+/-3 days)
bevacizumab	10 mg/ kg IV q 2 weeks	IV**	1,15	Q 28 days (+/-3 days)

*Pre-Medication: Diphenhydramine 25-50 mg I.V. (or comparable antihistamine) approximately 30 minutes before starting temsirolimus infusion.

**The first dose of bevacizumab should be given over 90 minutes. If well tolerated, second dose may be administered over 60 minutes. Again, if well tolerated, subsequent doses may be administered over 30 minutes.

Temsirolimus will be given first followed by bevacizumab on days 1 and 15 of each cycle. One cycle is defined as 4 weeks (i.e. 28 days) of treatment.

5.1 b Study Drug Administration single agent Bevacizumab Islet cell cohort

Agent	Dose	Route	Day	ReRx
bevacizumab	10 mg/ kg IV q 2 weeks	IV**	1,15	Q 28 days (+/-3 days)

**The first dose of bevacizumab should be given over 90 minutes. If well tolerated, second dose may be administered over 60 minutes. Again, if well tolerated, subsequent doses may be administered over 30 minutes.

5.2 Ancillary Treatment/Supportive Care

5.21 Requirement for radiation therapy during treatment is not allowed, as it is an indication of progressive disease.

5.22 Pain medications are allowed.

5.23 Antiemetic therapy is allowed.

5.24 Zoledronic acid can be continued in patients with bone metastases and/or hypercalcemia if it was started prior to treatment initiation.

5.25 Bevacizumab specific general patient monitoring and supportive care guidelines:

5.251 Patients should be carefully monitored during the treatment phase and then followed appropriately. Prior to each treatment, the patient should be carefully assessed, with special attention to blood pressure and bleeding events as well as other adverse events. Decisions for retreatment or dose modifications/interruption should follow the guidelines in Section 6.0.

5.252 Patients who have an on-going study agent-related serious adverse event upon study completion or at discontinuation from the study will be contacted by the investigator or his/her designee periodically until the event is resolved or determined to be irreversible.

5.253 Hypertension: Blood pressure should be assessed at least weekly during the first cycle and before each administration of bevacizumab. High blood pressure may require initiation or increase in hypertensive medication according to routine practice. Bevacizumab treatment modifications due to hypertension should follow instructions in Section 6.0.

5.254 Therapeutic anticoagulation: For patients on therapeutic anticoagulation, PT INR or PTT (which ever appropriate) should be monitored closely during bevacizumab therapy. Bevacizumab should be held if the coagulation parameters are higher then the intended therapeutic range (see Section 6.0).

5.255 Surgery and wound complication issues and surgery: The appropriate interval from discontinuation of bevacizumab to subsequent elective surgery required to reduce the risk of impaired wound healing has not been determined. Decision on such an interval should take into consideration the half-life of bevacizumab. It is generally recommended that bevacizumab should be discontinued at least 4-8 weeks prior to major elective surgery. In addition, bevacizumab should not be restarted until at least 4 weeks after major surgery provided that the wound has adequately healed; in cases of high risk procedures such as liver

resection, thoracotomy or neurosurgery, it is recommended that bevacizumab be resumed no earlier than 8 weeks after surgery.

5.26 Temsirolimus specific general patient monitoring and supportive care guidelines:

5.261 Temsirolimus is a CYP3A4 substrate. Avoid concomitant treatment of temsirolimus with potent CYP3A4 inhibitors and agents that have CYP3A4 induction potential. (Appendix D)

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s) felt to be study drug-related, treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Treatment delay of greater than 4 weeks
- Withdrawn consent
- Changes in the patient's condition render the patient unacceptable for further treatment in investigator's judgment.
- Need for radiation therapy for symptomatic disease.

5.4 Duration of Follow Up

Patients will be followed for three years from registration or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6. DOSING DELAYS/DOSE MODIFICATIONS

Strictly follow the modifications in this table for all cycles
ALERT: *ADR reporting may be required for some adverse events (See Section 7)*

6.1 Bevacizumab Related Adverse Events

CTCAE CATEGORY	ADVERSE EVENT	DOSAGE CHANGE
Hemorrhage/ Bleeding	Hemorrhage: CNS or pulmonary Grade 1 on anticoagulation	Discontinue bevacizumab
	Hemorrhage: CNS or pulmonary ≥ Grade 2	Discontinue bevacizumab

	Any Grade 3 other than CNS or pulmonary	• Patients who are also receiving full-dose anticoagulation should discontinue bevacizumab
		• All other patients should have bevacizumab omitted until ALL of the following criteria are met:
		  • The bleeding has resolved and Hb is stable.
		  • There is no bleeding diathesis that would increase the risk of therapy
		  There is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence
		  • Patients who experience recurrence of G3 hemorrhage should discontinue study therapy

	Any Grade 4 other than CNS pulmonary	Discontinue bevacizumab
Vascular	Grade 3 or Asymptomatic Grade 4: Symptomatic Grade 4:	Omit bevacizumab treatment. If the planned duration of full-dose anticoagulation is ≤2 weeks, bevacizumab should be omitted until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: – The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions) – The subject must not have had hemorrhagic events while on study – The subject must on stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. Discontinue bevacizumab
Coagulation	APTT (INR)	For patients on therapeutic anticoagulation, PT INR or PTT (which ever appropriate) should be monitored closely during bevacizumab therapy. bevacizumab should be omitted if the coagulation parameters are higher then the intended therapeutic range

Cardiac general	Hypertension Grade ≤ 3 Grade 4	Hypertension should be treated with anti-hypertensive medication as per general practice. For controlled hypertension: continue therapy. For persistent or symptomatic hypertension: omit bevacizumab therapy. If treatment is delayed for >4 weeks due to uncontrolled hypertension, patients should discontinue bevacizumab.
	Congestive Heart Failure Grade 3 (symptomatic) Grade 4	 Discontinue bevacizumab Discontinue bevacizumab
Metabolic/ Laboratory	 < 2 g/24 hours ≥ 2 g/24 hours Grade 4: (nephrotic syndrome)	Proteinuria should be monitored by urine analysis for urine protein prior to every other dose of bevacizumab • Continue bevacizumab. • Omit bevacizumab until urine protein recovers to ≤ 2 g/24 hours Discontinue bevacizumab
Dermatology/ skin	Wound complication, non-infectious Wound dehiscence requiring medical or surgical intervention: Any Grade	Discontinue bevacizumab
Gastrointestinal	Bowel perforation, fistula or GI leak: any grade (GI or any other organ)	Discontinue bevacizumab
	Bowel obstruction Grade 2 (requiring medical intervention) Grade 3-4	 Omit bevacizumab until complete resolution Omit bevacizumab until complete resolution. If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion
Neurology	Symptoms and signs of RPLS	Omit pending workup and management, including control of blood pressure. Discontinue if RPLS diagnosed. Resumption of bevacizumab may be considered in patients who have documented benefit from the agent, provided that RPLS was mild and has completely resolved clinically and radiographically within 2-4 weeks; decision to resume bevacizumab in these patients must be discussed with the study chair and approved by the sponsor.
Other	Grade 3 -non-hematological (except nausea and vomiting) Grade 4 non-hematological (except nausea/vomiting) Grade 4 hematological (any cause)	If a patient develops any grade 3 non-hematological adverse events. bevacizumab should be omitted until symptoms resolve to ≤grade 1. If a grade 3 adverse event persists for >4 weeks or recurs after resumption of the therapy, discontinue bevacizumab and patient should go to event monitoring. The patient should discontinue bevacizumab. Omit until recover to § ANC >1.0 × 10^9/L (1000 cells/mm^3)

		▪ Platelet count >50 × 10^9/L (50,000 cells/mm^3)

6.2 Temsirolimus Related Adverse Events

NCI CTC Grade		TEMSIROLIMUS
0-2 Hematological or Non-hematological Toxicity		100% Grade 2 adverse events that are persistent and intolerable ≥ 7 days (i.e. stomatitis) can result in omission or dose reductions to the next lower dose level
3 Hematological or non-hematological Toxicity		Omit until recovery to § ANC ≥1.0 × 10^9/L (1000 cells/mm^3) ▪ Platelet count ≥50 × 10^9/L (50,000 cells/mm^3) ▪ Or NCI CTC Grade 0-2 for non-hematologic If recovery occurs within 3 weeks after treatment has been omitted, dose should be reduced 1 level
4 Hematological or non-hematological Toxicity		Omit until recover to § ANC ≥1.0 × 10^9/L (1000 cells/mm^3) ▪ Platelet count ≥50 × 10^9/L (50,000 cells/mm^3) ▪ Or NCI CTC Grade 0-2 for non-hematologic If recovery occurs within 3 weeks after treatment has been omitted, dose should be reduced 2 levels
Metabolic/Laboratory	Cholesterol, serum high (hypercholesterolemia) ≥ Grade 3 Triglyceride, serum high (hypertriglyceridemia) Grade 1 and 2	May continue treatment. Start or adjust dosage of antihyperlipidemic agents. If baseline levels, < grade 2 hypertriglyceridemia, or ≤ grade 2 hypercholesterolemia, whichever is higher, are not achieved after 8 weeks, discontinue agent.
	Triglyceride, serum high (hypertriglyceridemia) ≥ Grade 3	Omit temsirolimus for 1 week. Therapy with a triglyceride-lowering agent will be initiated. Triglycerides will be re-assessed at the end of the week, and temsirolimus will be resumed if the triglycerides level is reduced to Grade ≤ 2. If triglycerides remain at grade 3 or 4 levels, temsirolimus will be omitted another week, with serum triglycerides re-assessed one week later. If a patient's triglyceride levels remain at CTCAE grade 3-4 for two weeks despite triglyceride-lowering therapy, discontinue agent. If Grade 3 or 4 hypertriglyceridemia recurs after re-challenge, dose interruption will be managed as above, and the patient will resume therapy at a dose reduction of 2 dose levels if the hypertriglyceridemia resolves to a Grade ≤ 2 level within 2 weeks.
Hemorrhage	CNS/Pulmonary hemorrhage ≥ Grade 2	Discontinue temsirolimus
Pulmonary/Upper Respiratory Addendum 1	pneumonitis	Patients with cough and dyspnea should have temsirolimus omitted pending investigation and permanently discontinued if the diagnosis is confirmed and thought to be related to temsirolimus.
Vascular	Grade 3 or Asymptomatic Grade 4:	Omit temsirolimus treatment. If the planned duration of full-dose anticoagulation is ≤2 weeks, temsirolimus should be omitted until the full-dose anticoagulation period is over. If anticoagulation of > 2 weeks then temsirolimus may be

		restarted when patients have been on a stable dose of anticoagulant for at least 1 week.

Dose Reductions for temsirolimus Related Adverse Event

Dose Level	temsirolimus Dose (mg)
Starting dose	25
-1	20
-2	15
-3	10

Patients requiring dose reductions should not have the dose re-escalated with subsequent treatments.

If one of the agents is discontinued, patients can continue on study and receive the other agent.

HCC Patients only:

Decompensation to Child-Pugh B or C liver status	If thought likely to be drug related bevacizumab and temsirolimus should be omitted until patient returns to Child-Pugh A status. (All appropriate supportive care offered) bevacizumab can be re-started at full dose while temsirolimus will restart at 1 further dose reduction. If decompensation due to progressive disease patient will come off treatment and go to event monitoring.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 CTCAE v 3.0

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 for adverse event (AE) monitoring and reporting. The CTCAE v3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov/reporting/ctc.html). All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

7.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE. Next, determine whether the event is expected or unexpected (as reflected with the CTEP Agent Specific Adverse Event List [ASAEL], see Section 7.12) and if the adverse event is related to the medical treatment or procedure (see Section 7.13). With this information, determine whether an adverse event should be reported as an expedited report (see Section 7.2) or as part of the routinely reported clinical data (see Sections 7.2 and 16.3). AEs reported as expedited must also be reported in routine study data submissions.

Expedited adverse event reporting under a CTEP Investigational New Drug Application (IND) requires submission of an CTEP Adverse Event Expedited Reporting System (CTEP-AERS) report(s). Other expedited reporting requirements and systems may also apply. Expedited reports are to be completed within the timeframes and via the mechanisms specified in Section 7.2.

In the rare occurrence when Internet connectivity is lost, an AE report may be submitted using CTEP's Adverse Event Expedited Report-Single Agent or Multiple Agent paper template (available at http://ctep.cancer.gov) and faxed to 301-230-0158. A 24-hour notification is to be made to CTEP by telephone at 301-897-7497, **only** when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted on paper or a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the local institution.

ALL expedited reports submitted via the secure CTEP-AERS application must also be copied to the P2C Coordinating Center Quality Control Specialist for this protocol (for MC0845) via fax (507-266-7240).

Those AEs that do not require expedited reporting will be reported to CTEP in routine (CDUS) study data submissions by the CTSU Data Operations Center. Therefore, AEs reported through CTEP-AERS must **also** be reported in routine study data submissions to CTSU Data Operations Center (see Sections 7.2 and 16.3).

7.12 Expected vs. Unexpected Events

Agents provided under a CTEP IND:

- Expected AEs for expedited reporting purposes are listed on the ASAEL. The ASAEL is a component of the Comprehensive Adverse Events and Potential Risks List (CAEPR). Refer to Section 15.0 of this protocol to locate the CAEPR for the CTEP IND agent(s).
- Unexpected AEs are those not listed in the ASAEL.

7.13 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the investigational agent(s).
Probable - The adverse event *is likely related* to the investigational agent(s).
Possible - The adverse event *may be related* to the investigational agent(s).
Unlikely - The adverse event *is doubtfully related* to the investigational agent(s).
Unrelated - The adverse event *is clearly NOT related* to the investigational agent(s).

7.2 Expedited Adverse Event Reporting Requirements

7.21 CTEP Expedited AE Investigational Agent Reporting Requirements

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: CTEP-AERS Reporting Requirements for Adverse Events That Occur Within 30 Days [1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 [2]	Grades 4 & 5 [2]
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report

is required as outlined in the table.

December 15, 2004

Note: All deaths on study must be reported using expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

ALL expedited reports submitted to CTEP must be simultaneously copied to the Coordinating Center Control Specialist (for MC0845) via fax (507-266-7240).

7.22 Other Required Reporting

EVENT	*REPORTING PROCEDURE*
Secondary AML/MDS	*Reporting for this event required during and after completion of study treatment.* ***Submit the NCI/CTEP Secondary AML/MDS Report form within 10 days via fax to the Coordinating Center Quality Control Specialist (for MC0845) (507-266-7240).***
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Reportable	Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form within 5 working days. If CTEP-AERS or other expedited report has been submitted, this form does not need to be submitted. **Fax to the Coordinating Center Quality Control Specialist (MC0845)via fax (507-266-7240).**

7.3 Exclusions from Expedited Reporting

For this protocol, the following adverse events are specifically excluded from expedited AE reporting:

CTCAE Category	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Comments
Blood/Bone marrow	↓Hemoglobin, leukocytes (total WBC), lymphopenia, ↓neutrophils/ granulocytes (ANC/AGC), ↓platelets	1-3	No	These AEs do not require expedited reporting unless patient is hospitalized for management
Gastrointestinal	Diarrhea, nausea, vomiting, stomatitis	1-3	Yes	Hospitalization for grade 3 AEs does not require expedited reporting. Complications from these GI adverse events such as dehydration, and electrolyte abnormalities do not require expedited reporting unless grade 4 and patient hospitalized for management
Metabolic/laboratory	Hypercholesterolemia, hyperglycemia, hypertriglyceridemia	1-3	No	These AEs do not require expedited reporting unless patient is hospitalized for management

7.4 Adverse Events to be Graded

Pretreatment symptoms/conditions to be evaluated at baseline and each evaluation per Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grading unless otherwise stated in the table below:

Category	Adverse Events/Symptoms	Baseline	Each evaluation
Cardiac- general	Hypertension		X
	Cardiac ischemia/infarction		X
Hemorrhage /Bleeding	Hematoma		X
	Hemorrhage, GI -Lower GI NOS -Upper GI NOS		 X X
	Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)		X
	Hemorrhage, pulmonary/upper respiratory -Lung		X
Infection	Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)		X
Metabolic/ laboratory	Bilirubin (hyperbilirubinemia)	X	X
	Cholesterol, serum-high (hypercholesteremia)	X	X
	Proteinuria	X	X
Neurology	Leukoencephalopathy (radiographic findings)		X
Vascular	Thrombosis/thrombus/embolism	X	X*

* Specify venous or arterial.

7.41 Documentation of the following AEs, when experienced by a participant but not specified in Section 7.3, are to be submitted using data collection mechanisms described in Section 16.0:

7.411 Grade 1 and 2 AE's deemed possibly, probably, or definitely related to the study treatment or procedure.

7.412 Grade 3 and 4 AE's regardless of attribution to the study treatment or procedure.

7.413 Grade 5 AE's (Deaths)

7.4131 Any death within 30 days of a patient's last treatment, regardless of relationship to study treatment or procedure.

7.4132 Any death more than 30 days after the participant's last study treatment or procedure which is felt to be at least

possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

7.42 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AE's following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule Section 10.0).

8. PHARMACEUTICAL INFORMATION

8.1 Temsirolimus (Torisel®) (NSC # 683864)

Pharmaceutical Information

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 8.13.

Temsirolimus (Torisel®) (NSC 683864)

Chemical Name: Sirolimus 42-ester with 2,2-bis (hydroxymethyl)-propionic acid

Other Names: temsirolimus, Torisel®, Rapamycin analog, WAY-130779

Classification: Cell cycle inhibitor

Molecular Formula: $C_{56}H_{87}NO_{16}$ **M.W.:** 1030.30 Daltons

Mode of Action: Temsirolimus [an ester of the immunosuppressive compound sirolimus, (rapamycin, Rapamune®)] blocks cell cycle progression from the G1 to the S phase by binding to the intracellular cytoplasmic protein, FK506 binding protein (FKBP) 12. This complex inhibits activity of the enzyme mTOR (mammalian target of rapamycin), inhibiting translation of several key proteins that regulate progression through the G1 phase in response to growth factors. Sirolimus, temsirolimus' s major metabolite, also binds to FKBP12.

How Supplied: TORISEL (temsirolimus) is supplied as a commercially labeled kit consisting of the following:

- TORISEL (temsirolimus) injection (25 mg/mL). The TORISEL vial includes an overfill of 0.2 mL. Inert ingredients in the drug vial include dehydrated alcohol, d,l-alpha-tocopherol, propylene glycol, and anhydrous citric acid.

DILUENT for TORISEL. The DILUENT vial includes a deliverable volume of 1.8 mL. The diluent vial contains polysorbate 80 NF, polyethylene glycol 400 NF, and absolute alcohol USP.

Preparation: These mixing instructions apply to commercial TORISEL only. The investigationally labeled product is mixed differently.

Protect from excessive room light and sunlight during preparation.

Follow this two step dilution process (TORISEL should only be diluted with the supplied diluent):

Step 1
Inject 1.8 mL of DILUENT for TORISEL into the vial of TORISEL injection (25 mg/mL). Due to the intentional 0.2 mL overfill in the TORISEL injection vial, the resulting drug concentration will be 10 mg/mL. A total volume of 3 mL will be obtained. Mix well by gentle inversion of the vial. DO NOT SHAKE. Allow sufficient time for air bubbles to subside.

Step 2
Withdraw the required amount of TORISEL from the 10 mg/mL drug solution/diluent mixture prepared in Step 1. Further dilute with 0.9% sodium chloride injection immediately in glass or polyolefin containers to a final concentration between 0.04 mg/mL and 1 mg/mL.

Storage: Refrigerate intact TORISEL kit at 2º-8ºC and protect from light.

Stability: The 10 mg/mL drug solution/diluent mixture is stable for 24 hours at room temperature.

Administer within 6 hours of the final dilution in 0.9% NaCl.

Route of Administration: Intravenous with an appropriate in-line filter (i.e. 0.2 to 5 micron) for all temsirolimus doses equal to or greater than 10 mg. Do not use an inline filter for temsirolimus doses less than 10 mg. Do not expose to direct sunlight during administration.

Incompatibilities: Avoid contact of the diluted product with polyvinyl chloride (PVC) equipment or devices that are plasticized with di- (2-ethylhexyl)pthalate (DEHP) to prevent DEHP leaching. Store diluted temsirolimus solutions in bottles (glass) or plastic bags (polyolefin or polypropylene).

Temsirolimus is compatible with most infusion sets that are acceptable with paclitaxel.

Infusion sets which have been qualified for use with temsirolimus include the following:

- •Baxter vented paclitaxel set
- •Baxter unvented paclitaxel set
- •Abbott #11947 tubing set
- •Alaris #72953 tubing set

Other non-PVC tubings can be used with the following in-line filters:

- •IV 6200 Disposable I.V. Filter 0.2 micron by EPS®, Inc
- •IV 6120 Disposable I.V. Filter 1.2 micron by EPS®, Inc
- •LV 5000 Large Volume 5 micron Conical Filter by B.Braun
- •Baxter Paclitaxel IV 0.2 micron filter set (2C7555)
- •Codan 5 micron monofilter
- •Alaris extension filter set #20350E

Other polyethersulfone filters may be used.

Potential Drug Interactions:

The combination of temsirolimus and sunitinib resulted in dose limiting toxicity at low doses of both agents. Avoid concomitant sunitinib during temsirolimus treatment.

Temsirolimus and warfarin may interact to increase INR. Monitor warfarin patient's PT/INR after starting and stopping temsirolimus.

The combination of temsirolimus and ACE inhibitors resulted in angioedema-type reactions (including delayed reactions occurring up to 2 months after initiation of therapy).

Patient Care Implications:

For hypersensitivity prophylaxis, give diphenhydramine 25-50 mg orally or by I.V. (or comparable antihistamine) approximately 30 minutes before starting temsirolimus infusion. Infuse over 30 minutes.

If a patient develops a hypersensitivity reaction despite diphenhydramine pretreatment, stop the infusion and wait 30 to 60 minutes (depending upon the reaction severity). At the physician's discretion, it may be possible to resume treatment by administering an H2 blocker approximately 30 minutes before restarting the infusion. The manufacturer recommends famotidine 20 mg IV, rather than cimetidine, because it lacks reported drug interactions. Re-attempt infusion at a slower rate, possibly over one hour.

Vaccinations: Avoid the use of live vaccines during temsirolimus treatment.

8.12 Availability

temsirolimus
Temsirolimus is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Temsirolimus is provided to the NCI under a Cooperative Research and Development Agreement (CRADA) between Wyeth Pharmaceuticals, Inc. and the DCTD, NCI.

8.13 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Temsirolimus (CCI-779, NSC 683864)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1927 patients.* Below is the CAEPR for temsirolimus (CCI-779, Torisel).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, July 2, 2013[1]

Adverse Events with Possible Relationship to Temsirolimus (CCI-779, Torisel) (CTCAE 4.0 Term) [n= 1927]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
ENDOCRINE DISORDERS			
	Endocrine disorders - Other (decreased testosterone)		***Endocrine disorders - Other (decreased testosterone) (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal distension		***Abdominal distension (Gr 2)***
	Abdominal pain		***Abdominal pain (Gr 3)***
	Anal mucositis[2]		***Anal mucositis[2] (Gr 2)***
	Constipation		***Constipation (Gr 3)***

Diarrhea			***Diarrhea (Gr 3)***
		Gastrointestinal fistula[3]	
		Gastrointestingal perforation[4]	***Gastrointestinal perforation[4] (Gr 2)***
Mucositis oral[2]			***Mucositis oral[2] (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Rectal mucositis[2]		***Rectal mucositis[2] (Gr 2)***
	Small intestinal mucositis[2]		***Small intestinal mucositis[2] (Gr 2)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema face		***Edema face (Gr 2)***
	Edema limbs		***Edema limbs (Gr 3)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Flu like symptoms		***Flu like symptoms (Gr 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 2)***
	Pain		
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[5]		***Allergic reaction[5] (Gr 2)***
INFECTIONS AND INFESTATIONS[6]			
	Infection[7]		***Infection[7] (Gr 3)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Wound dehiscence[8]		***Wound dehiscence[8] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
Cholesterol high[9]			***Cholesterol high[9] (Gr 4)***
	Creatinine increased		***Creatinine increased (Gr 3)***
	Fibrinogen decreased		***Fibrinogen decreased (Gr 2)***
	GGT increased		***GGT increased (Gr 2)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased[10]		***Neutrophil count decreased[10] (Gr 4)***
Platelet count decreased[10]			***Platelet count decreased[10] (Gr 4)***
	Weight loss		***Weight loss (Gr 3)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Acidosis		***Acidosis (Gr 2)***
Anorexia			***Anorexia (Gr 3)***
	Glucose intolerance[11]		***Glucose intolerance[11] (Gr 2)***
	Hyperglycemia[11]		***Hyperglycemia[11] (Gr 3)***
	Hypertriglyceridemia[9]		***Hypertriglyceridemia[9] (Gr 4)***
	Hypocalcemia		***Hypocalcemia (Gr 3)***
	Hypokalemia		***Hypokalemia (Gr 4)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
	Metabolism and nutrition disorders - Other (hyperlipidemia)[9]		***Metabolism and nutrition disorders - Other (hyperlipidemia)[9] (Gr 4)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***

	Myalgia		***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Depressed level of consciousness		***Depressed level of consciousness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 3)***
PSYCHIATRIC DISORDERS			
	Depression		***Depression (Gr 2)***
	Insomnia		***Insomnia (Gr 2)***
	Libido decreased		***Libido decreased (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury[12]	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
	Erectile dysfunction		***Erectile dysfunction (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		***Epistaxis (Gr 2)***
	Laryngeal mucositis[2]		***Laryngeal mucositis[2] (Gr 2)***
	Pharyngeal mucositis[2]		***Pharyngeal mucositis[2] (Gr 2)***
	Pleural effusion		***Pleural effusion (Gr 3)***
	Pneumonitis[13]		***Pneumonitis[13] (Gr 3)***
	Sinus disorder		***Sinus disorder (Gr 2)***
	Tracheal mucositis[2]		***Tracheal mucositis[2] (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		***Dry skin (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
	Rash acneiform		***Rash acneiform (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous tissue disorders – Other (nail disorder/nail changes)[15]		***Skin and subcutaneous tissue disorders – Other (nail disorder/nail changes)[15] (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
	Hypotension		***Hypotension (Gr 3)***
		Thromboembolic event	***Thromboembolic event (Gr 4)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Mucositis/stomatitis: Gingivitis, mucositis/stomatitis, ulcers in mouth and throat, pharyngitis, and dysphagia have been reported in subjects receiving temsirolimus.

[3]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC. GI perforation (including fatal outcome) has been observed in subjects who received temsirolimus.

[5]Hypersensitivity /infusion reactions (including some life threatening and rare fatal reactions), including and not limited to flushing, chest pain, dyspnea, hypotension, apnea, loss of consciousness, hypersensitivity, and anaphylaxis, have been associated with the administration of temsirolimus. These reactions can occur very early in the first infusion, but may also occur with subsequent infusions. Patients should be monitored early during infusion and appropriate supportive care should be available. Temsirolimus infusion should be interrupted in all patients with severe infusion reactions and appropriate medical care administered. A risk-benefit assessment should be done prior to the continuation of temsirolimus therapy in patients with severe life-threatening reactions.

[6]Infections: Bacterial and viral infections including opportunistic infections have been reported in subjects. Infections may originate in a variety of organ systems/body regions and may be associated with normal or grade 3-4 neutropenia. Bacterial and viral infections have included cellulitis, herpes zoster, herpes simplex, bronchitis, abscess, pharyngitis, urinary tract infection (including dysuria hematuria, cystitis, and urinary frequency), rhinitis folliculitis, pneumonia, and upper respiratory tract infection.

[7]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[8]Wound Dehiscence: The use of temsirolimus has been associated with abnormal wound healing. Therefore, caution should be exercised with the use of temsirolimus in the perisurgical period.

[9]Cholesterol High: The use of temsirolimus in subjects has been associated with increases in serum levels of triglycerides and cholesterol. This may require initiation of or increase in the dose of lipid-lowering agents.

[10]Thrombocytopenia and Neutropenia: Grades 3 and 4 thrombocytopenia and/or neutropenia have been observed at higher frequency in subjects with mantle cell lymphoma (MCL).

[11]Hyperglycemia/Glucose Intolerance: The use of temsirolimus in subjects was associated with increases in serum glucose level. This may result in the need for an increase in the dose of, or initiation of, insulin and/or oral hypoglycemic agent therapy.

[12]Acute Kidney Injury: Renal failure (including fatal outcome) has been observed in subjects receiving temsirolimus for advanced RCC and/or with pre-existing renal insufficiency.

[13]Interstitial Lung Disease: There have been cases of nonspecific interstitial pneumonitis, including rare fatal reports. Some subjects were asymptomatic with pneumonitis detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnea, cough, and fever. Some subjects required discontinuation of temsirolimus or treatment with corticosteroids and/or antibiotics, while some subjects continued treatment without additional intervention.

[14]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[15]Nail Disorder/Nail Changes includes Nail discoloration, Nail loss, and Nail ridging under the SKIN AND SUBCUTANEOUS TISSUE DISORDERS SOC.

Also reported on temsirolimus (CCI-779, Torisel) trials but with the relationship to temsirolimus (CCI-779, Torisel) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (coagulopathy); Hemolysis; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Chest pain - cardiac; Heart failure;

Left ventricular systolic dysfunction; Myocardial infarction; Pericardial effusion; Right ventricular dysfunction; Sinus tachycardia; Supraventricular tachycardia; Ventricular fibrillation; Ventricular tachycardia

EAR AND LABYRINTH DISORDERS - Vertigo

ENDOCRINE DISORDERS - Endocrine disorders - Other (Cushing's syndrome); Endocrine disorders - Other (diabetes mellitus)

EYE DISORDERS - Blurred vision; Cataract; Conjunctivitis; Dry eye; Eye disorders - Other (diplopia); Eye pain; Flashing lights; Photophobia; Retinopathy

GASTROINTESTINAL DISORDERS - Anal pain; Anal ulcer; Ascites; Bloating; Colitis; Colonic obstruction; Colonic ulcer; Dry mouth; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophageal pain; Esophageal ulcer; Esophagitis; Flatulence; Gastritis; Gastrointestinal disorders - Other (anal fissure); Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal disorders - Other (mouth ulceration); Gastrointestinal hemorrhage[14], Hemorrhoids; Ileus; Oral pain; Pancreatitis; Periodontal disease; Proctitis; Rectal pain; Small intestinal obstruction; Stomach pain; Typhlitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema trunk; Facial pain; Gait disturbance; Injection site reaction; Localized edema; Malaise; Multi-organ failure; Sudden death NOS

HEPATOBILIARY DISORDERS - Hepatic failure

IMMUNE SYSTEM DISORDERS - Anaphylaxis

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Fracture; Postoperative hemorrhage; Vascular access complication; Wound complication

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; CD4 lymphocytes decreased; INR increased (potential interaction with Coumadin); Investigations - Other (BUN increased); Investigations - Other (lactic dehydrogenase increased); Lipase increased; Lymphocyte count increased; Serum amylase increased; Weight gain

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hyperuricemia; Hypoalbuminemia; Hypoglycemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (albuminuria) ; Metabolism and nutrition disorders - Other (blood urea increased);
Metabolism and nutrition disorders - Other (hypoproteinemia)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Avascular necrosis; Bone pain; Chest wall pain; Generalized muscle weakness; Joint effusion; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle cramps); Neck pain; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (carcinoma of the lung); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lymphoma); Treatment related secondary malignancy

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Dizziness; Dysesthesia; Hydrocephalus; Intracranial hemorrhage; Lethargy; Neuralgia; Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Seizure; Somnolence; Spasticity; Stroke; Syncope

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Mania; Psychiatric disorders - Other (bipolar disorder); Psychosis

RENAL AND URINARY DISORDERS - Bladder spasm; Cystitis noninfective; Hematuria; Hemoglobinuria; Proteinuria; Renal hemorrhage; Urinary frequency; Urinary retention; Urinary tract pain; Urinary urgency

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Female genital tract fistula; Hematosalpinx; Irregular menstruation; Menorrhagia; Ovarian hemorrhage; Prostatic hemorrhage; Spermatic cord hemorrhage; Testicular disorder; Testicular hemorrhage; Testicular pain; Uterine hemorrhage; Vaginal discharge; Vaginal dryness; Vaginal fistula; Vaginal hemorrhage; Vaginal inflammation

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Bronchopulmonary hemorrhage; Bronchospasm; Hiccups; Hypoxia; Nasal congestion; Pharyngolaryngeal pain; Pleuritic pain; Productive cough; Pulmonary edema; Pulmonary fibrosis; Pulmonary hypertension; Respiratory failure; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Erythema multiforme; Hyperhidrosis; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Skin and subcutaneous tissue disorders - Other (angioneurotic edema); Skin ulceration; Stevens-Johnson syndrome

VASCULAR DISORDERS - Flushing; Phlebitis; Superficial thrombophlebitis; Visceral arterial ischemia

Note: Intracerebral Bleeding: Subjects with central nervous system (CNS) tumors (primary CNS tumors or metastases) and/or receiving anticoagulation therapy may be at an increased risk of intracerebral bleeding (including fatal outcomes) while receiving therapy with temsirolimus (CCI-779, Torisel).

Note: Temsirolimus (CCI-779, Torisel) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

8.14 Drug procurement: temsirolimus may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by fax (301) 480-4612 or mailed to the Pharmaceutical Management Branch, CTEP, DCTD, NCI, 9000 Rockville Pike, EPN Rm. 7149, Bethesda, MD 20892.

The Investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form. See the CTEP home page for Policy and Guidelines for Accountability and Storage of Investigational Drugs (http://ctep.info.nih.gov/Policies/AcctabilitystorageInvDrugs.htm).

8.15 Nursing guidelines

8.151 Hypersensitivity reactions have been observed in some patients shortly after beginning the temsirolimus infusion (and ending shortly after stopping the infusion). Signs and symptoms have included flushing of the face and neck (and in some cases also involving the extremities and trunk), description of feeling hot, uncomfortable, and/or anxious, chest pain/tightness, shortness of breath, decrease in oxygen saturation and cyanosis, hypotension, lightheadedness, periorbital puffiness, description of feeling like the patient's head was swelling, nausea, back pain, numbness and tingling of hands/feet/face, and difficulty speaking. Some patients have been able to receive subsequent infusions following pre-medication with diphenhydramine with or without corticosteroids and/or histamine H_2-receptor antagonist. Pre-medication with diphenhydramine now is being used in all new patients to try to prevent the occurrence of these reactions. If a patient begins to develop a hypersensitivity reaction despite pretreatment with diphenhydramine, the infusion should be stopped. It may be possible to resume treatment after waiting at least 30-60 minutes (depending upon the severity of the reaction) by administering a

histamine H_2-receptor antagonist approximately 30 minutes before restarting the temsirolimus infusion. Famotidine 20 mg IV is the recommended agent. The rate of the temsirolimus infusion also may be slowed, administered over 1 hour. All patients should be monitored closely while receiving the temsirolimus infusion.

8.152 Treat stomatitis symptomatically – may try dabbing vitamin E oil on lesions. Do not swallow oil. Advise frequent and careful oral hygiene.

8.563 Drug may cause hypocalcemia and/or hypophosphatemia. Instruct patient to report any persistent muscle aching, muscle weakness, nocturia, or polyuria. Encourage hydration.

8.154 Monitor CBC closely. Instruct patient to report any signs or symptoms of infection. The degree of immunosuppression may be enhanced if corticosteroids are being used concurrently.

8.155 Instruct patient to report any unusual and/or persistent bruising or bleeding to the health care team.

8.156 Headache may occur. Tylenol may benefit. Instruct patient to report any headache that is not relieved.

8.157 Libido may be affected and sexual performance may be affected. Patients and their partners may wish to discuss intimacy issues.

8.157 Assess patient's list of medications (including OTC drugs) closely. Patient should avoid taking any medications that inhibit or induce the CYP3A pathway of the P450 system. Instruct patient that they should check with the health care team before starting any new medication, including over the counter medications.

8.159 Nausea and vomiting may occur. Administer antiemetics as ordered and assess for their effectiveness.

8.160 Diarrhea may also occur. Administer antidiarrheals as needed and assess for their effectiveness.

8.161 Monitor cholesterol and triglyceride levels.

8.162 Instruct diabetic that hyperglycemia may occur. Blood glucose should be monitored closely and any uncontrolled episodes of hyperglycemia should be reported to the health care team immediately.

8.163 Instruct patient to report rash to the health care team immediately.

8.164 Instruct patient to report any cough, shortness of breath or chest pain to the health care team.

8.165 Because the risk of cardiovascular events is still undetermined, vital signs should be monitored prior to, during, and after the infusion closely, per individual institution guidelines.

8.166 Monitor liver and renal function tests.

8.167 Patient may develop dry skin and or dry eyes. Advise patient to use moisturizing lotions and/or tears.

8.168 Instruct patients to report episodes of epistaxis. Minor episodes may be dealt with at home by applying ice packs, and keeping head back. More serious episodes may have to be dealt with in the ER.

8.2 Bevacizumab (Avastin®) (NS C 704865)

Other Names: rhuMAb VEGF, Avastin®

Classification: Recombinant humanized monoclonal antibody

Molecular Weight: Approximate molecular weight is 149,000 Daltons

Mode of Action: Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.

Description: Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions

How Supplied: Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid for parenteral administration. Each 400 mg (25mg/ml - 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate20, and Sterile Water for Injection, USP.

Preparation: Vials contain no preservatives and are intended for single use only. Place the calculated dose in 100 mL of 0.9% sodium chloride for injection.

Storage: Upon receipt, refrigerate bevacizumab (2 to 8 C). Do not freeze. Do not shake.

Stability: Shelf-life studies of rhuMAb VEGF are ongoing. The sterile single use vials contain no antibacterial preservatives. Discard vials 8 hours after initial entry.

Once diluted in 0.9% sodium chloride, administer solutions of bevacizumab within 8 hours.

Route of Administration: Intravenous

Method of Administration: Administer the initial dose over a minimum of 90 minutes. If no adverse reactions occur, administer the second dose over a minimum of 60 minutes. If no adverse reactions occur after the second dose, administer subsequent doses over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

To insure complete delivery of bevacizumab, flush the IV infusion line with 0.9% sodium chloride. The following are two recommended methods for flushing the bevacizumab IV infusion line:
1. When the bevacizumab infusion is complete, add an additional 50mL of 0.9% sodium chloride for injection to the bevacizumab infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.
2. Replace the empty bevacizumab infusion bag with a 50mL bag of 0.9% sodium chloride for injection and infuse a volume equal to the volume contained in the tubing.
Please note: the flush is not included in the total recommended infusion times.

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8.23 Nursing Guidelines:

8.231 Monitor patients closely for infusion type reactions, including fever, chills, myalgias, rigors, or other allergic reactions. While this is less likely given that bevacizumab is a humanized antibody, there still exists the potential for severe allergic reactions. If these signs or symptoms occur stop the infusion immediately and contact MD. Have emergency equipment nearby and be prepared to administer emergency treatment as ordered by MD.

8.232 Monitor urine dipstick per protocol test schedule.

8.233 Evaluate IV site regularly for signs of infiltration.

8.234 Bleeding in the absence of thrombocytopenia is a dose limiting toxicity. Monitor patient closely for hemorrhagic events, including CNS hemorrhage, epistaxis, hematemesis and hemoptysis. Most cases of bleeding have occurred at the tumor site. Advise patient about the potential for bleeding or thrombosis.

8.235 In patients receiving treatment for lung cancer, hemoptysis and pulmonary hemorrhage occurred in up to 10% of patients in one study. Monitor these patients especially closely.

8.236 Patient may experience grade 1-2 nausea, however vomiting is uncommon. Medicate as ordered and monitor for effectiveness.

8.237 Monitor for skin rash, instruct patient to report to MD.

8.238 a Monitor blood pressure. Administer antihypertensives as ordered by MD.

8.239 aMonitor for signs and symptoms of deep vein thrombosis (DVT) or pulmonary embolism (PE), or myocardial infarction (MI) including new or worsening angina. These have been reported with therapy. Instruct patient to report any calf pain, chest pain or SOB to MD immediately.

8.239b Asthenia and headache were reported during therapy (in up to 70% and 50% of patients respectively). Administer acetaminophen as needed. Monitor for its effectiveness. Avoid the use of aspirin, or

ibuprofen as this may interfere with the coagulation cascade and further add to the risk of bleeding.

8.239c Monitor CBC, including platelets. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the MD.

8.239d Patient receiving warfarin therapy for thrombosis should have their PT or INR monitored weekly until two stable therapeutic levels are attained: for patients on warfarin for venous access prophylaxis, routine monitoring is satisfactory.

8.239e A rare but serious complication of bevacizumab is wound dehiscence. Patients who have had recent surgery or have other open wounds should be monitored carefully.

8.239f Gastrointestinal perforation with or without abdominal abscess is rare but possible. This may present itself as vague abdominal pain associated with constipation and vomiting. Instruct patient to report abdominal pain to the MD.

8.239g Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a rare (<1%) but serious condition. Presenting symptoms may include changes in mental status, visual disturbance, seizure, or other CNS changes. Patients with this syndrome generally had HTN as well, therefore BP monitoring is important. Instruct patient to report any mental status changes, visual changes, seizures, or other CNS changes to the MD immediately. These may be a sign of RPLS or more serious condition, such as hemorrhagic event in the CNS.

8.3 Agent Ordering/Accountability

8.31 Agent Ordering

NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied

investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Agent may be requested by completing a Clinical Drug Request (NIH-986) and mailing it to the Pharmaceutical Management Branch, DCTD, NCI, 9000 Rockville Pike, EPN Room 7149, Bethesda, MD 20892-7422 or faxing it to (301) 480-4612. For questions call (301) 496-5725.

8.32 Agent Accountability

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage and to obtain a copy of the DARF and Clinical Drug Request form.)

9. CORRELATIVE/SPECIAL STUDIES

A number of laboratory correlates could be proposed to be incorporated in this trial. However at this stage it is unclear whether there is added value in performing such studies. The primary rationale for performing such studies to determine whether there are potential predictive markers of clinical activity or toxicity for this combination. Since we do not know whether there will be sufficient activity of the combination that would enable such an analysis it is premature to propose the actual studies to be performed. Furthermore, there is little information available about the sensitivity, specificity, precision, day to day, within patient and between patient variability in clinical samples for many of the biomarkers one may wish to propose. Nevertheless, data on the assay characteristics of a number of such biomarkers may be gleaned from ongoing studies where biomarker analysis is being performed such as the kidney cancer trial being performed by the Mayo Clinic Consortium. Other single agent trials being performed under NCI auspices may generate additional information that may inform the assay characteristics. Thus we propose to collect, process and store genomic DNA, plasma, and archival tissue samples that will enable informed decisions to be made about what biomarkers would merit analysis. The actual analysis could be done by investigators who have obtained additional funding through a peer reviewed process. Such an application would have the information at hand of the clinical activity and/or toxicity of the combination. Possible markers that could be considered for analysis can include but are not limited to, tumor PTEN status, phospho Akt, serum VEGF, and sFLT levels, S6K and phospho S6K, cyclin D1, polymorphisms in drug metabolizing exzymes such as CYP3A4/5 and eNOS.

9.1 Laboratory Correlative Studies

9.1.1 Paraffin-embedded Blocks and Slides of primary tumors/metastases:

9.1.1.1 The clinical investigator and the submitting pathologist have the responsibility for submitting representative materials for the goals cited

in the protocol. The following materials are required for this protocol:

- At least one (two if possible) H&E stained slides with representative tumor.
- At least one (three, if possible) paraffin-embedded blocks with representative tumor.
- If an institution is unable to release tissue paraffin-embedded tissue blocks, they must be willing to submit 12 consecutive unbaked, unstained sections cut at 10 microns mounted on charged slides.

9.1.2 Blood sample collection

9.1.2.1 Samples will be collected processed and stored for biomarker studies related to the type of therapies used in this trial and the tumor types being treated. . One 7 ml EDTA tube of blood will be collected and centrifuged within 15 minutes. Plasma removed and stored at -70 until shipped. Buffy coat will be removed and stored at -70 until shipped. EDTA plasma and buffy coat should be shipped frozen on dry ice.

9.1.3 Sample Shipment

All specimens should be correctly labeled with patient initials, P2C study-specific subject ID number, date of birth, P2C protocol number, and date of collection. NOTE: In the event that baseline specimens are available but the patient is not successfully registered to the protocol, do not submit the patient's specimens. Specimens should be shipped frozen on a cold pack and must be shipped for express/overnight delivery.

Blood and Tissue Specimens:

Kits are required for the collection of blood and tissue specimens.

The kit contains supplies and instructions for collecting, processing, and shipping specimens. Collect and process all blood/blood products **and tissue,** according to specific kit instructions

Participating institutions may obtain kits by completing and faxing the Supply Order Form (found in both the Forms Packet) to the number listed on the form. Fill out the site address to where the kits will be shipped on the Fax Supply form. Because we are now being charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. Do not send the unused kits back to MML.

Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.** Kits will arrive inside the shipping boxes.

Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express service. **Mayo Clinic Cancer Center will <u>not</u> cover the cost for rush delivery of kits.**

All samples must be collected **Monday-Thursday ONLY.**

Label specimen tube(s) with protocol number, patient ID number, and time and date blood is drawn.

The MML kits will contain a smart shipper label (white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an airbill. Shipping costs will be covered by Mayo Clinic Cancer Center if this box is used fro shipping specimens to MML

Shipping blood specimens

Complete the Blood Specimen Submission Form, as appropriate, to document specimen submission in the study database.

Complete and verify ALL sections of the Blood Specimen Submission Form (see Forms Packet), MML Requisition Form (provided in kit), and specimen collection labels are completed and filled in correctly.

Blood specimens must be shipped the same day they are drawn. If specimens are collected on a Friday or a holiday, samples must be frozen at −20ºC or colder and shipped on the next normal working day (e.g., Monday). Avoid using a frost-free freezer, unless this is your only option.

Ship plasma and buffy coat specimens via Priority Overnight service, **Monday – Thursday ONLY,** to Mayo Medical Laboratories (MML) according to kit instructions. **Do not send samples on weekends or just prior to federal holidays.**

Processing of Blood Specimens

MML will receive the samples and immediately forward specimens to the Biospecimens Accessioning and Processing (BAP) Shared Resource, Stabile 13-10A, Attention: BAP Supervisor.

BAP will process specimens according to Appendix *G* instructions.

Shipping and Processing of Paraffin-embedded Blocks and/or Slides:

Complete the Tissue Specimen Submission Form, as appropriate, to document specimen submission in the study database.

Verify ALL sections of the Tissue Specimen Submission Form (see Forms Packet), MML Requisition Form (provided in kit), and specimen collection labels are completed and filled in correctly.

Ship ambient paraffin-embedded blocks and/or slides **according to the kit instructions and via ground service** to the following address:

P2C Operations Office
Attn: PC Office (Study MC0845)
RO_FF_03_24-CC/NW Clinic
200 First Street SW
Rochester MN 55905

Phone 507-293-3928

When an appropriate request is submitted, the Pathology Coordinator will forward the block/slides to the appropriate lab for processing.

10. STUDY CALENDAR

This schedule is based on currently available information regarding the study regimen and specifies the *minimum* procedures, exams, testing, etc., necessary to determine eligibility (baseline) and to evaluate safety and plan dose adjustments at subsequent cycles. The frequency of procedures may be increased or additional procedures performed as clinically indicated at physician discretion.

		Active Monitoring Phase		
Tests and procedures	≤7 days prior to registration	During interval between treatment	Prior to subsequent cycles	At PD, withdrawal or removal
History and exam, wt, PS, BP[6]	X		X	X
Height	X			
Hematology group WBC, ANC, Hemoglobin, platelets	X	X[3, 12]	X	X
Coagulation Prothrombin time, activated partial thromboplastin time, INR, fibrinogen	X		X[4]	
Chemistry group (fasting): glucose, total bilirubin, creatinine, alkaline phosphatase, SGOT (AST), ALT, Na, K, Ca, cholesterol, triglycerides,[13]	X		X	X
Urinalysis [5]	X[5]		X [5]	
LVEF assessment, if applicable[8]	X			
Chest x-ray (not required if chest CT was done)	X		X[4]	
Tumor Measurement/ Evaluation of indicator lesion (CT, MRI, etc.)[2]	X		X[2]	
Tumor Samples[7]	X			
Blood samples for banking [10, R]	X			
Serum pregnancy test[1]	X			
Islet cell and Carcinoid Cohorts Only: Measurement of relevant elevated circulating hormone level if applicable to each patient (e.g. serum glucagon, gastrin, Insulin, VIP, ACTH, chromagranin A, or 24 hr urinary 5-HIAA[11])	X		X[9]	
HCC Cohort: albumin, AFP	X		X	X
Ovarian Cohort: Mg, CA125	X		X	X

1. For women of childbearing potential only.
2. Baseline assessment may be ≤21 days prior to registration. Use the same method throughout the study. Followup scans to be performed every other cycle (8 weeks). If tumor measurement made by physical examination, must document prior to each cycle. Repeat measurements are required 4 weeks following a PR or CR. See Section 11.0 for full RECIST criteria. For Carcinoid cohort and Islet Cell cohort, Triple phase CT scan abd/pelvis or MRI of abdomen are recommended.
3. To be performed weekly (+/- 1 day).
4. As clinically indicated
5. Subjects discovered to have ≥2+ proteinuria at baseline or during study must undergo a 24-hour urine collection. This must be an adequate collection and must demonstrate <2 g of protein/24 hr to allow participation in the study. If proteinuria is found during the study, please see Table 6.1 for dose modification guidelines.
6. At least weekly during cycle 1, and prior to each administration of bevacizumab (per Section 5).
7. Tumor sample may be used from a previous surgery.
8. LVEF assessment ≤4 weeks prior to registration: required for patients who have received prior anthracycline, including doxorubicin and/or liposomal doxorubicin.
9. To be collected after every other cycle of treatment.
10. Collected after registration but prior to treatment.
11. 5-HIAA can be done ≤28 days

12. Hematology group not needed between cycles for patients in single agent bevacizumab Islet Cell Carcinoma cohort
13. Cholesterol and Triglycerides are not required for the Islet Cell-Bevacizumab only cohort.

R. Research funded.

11.0 Treatment Evaluation Using RECIST (version 1.1) Criteria[93]

11.1 Schedule of Evaluations

For the purposes of this study, patients should be reevaluated every 8 weeks. Determination of progression will be made according to the RECIST (version 1.1) criteria.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable disease is defined as at least one lesion whose longest diameter can be accurately measured as ≥2.0 cm with chest X-ray or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

11.22 Nodes with a short axis of ≥1.5 cm by CT are considered measurable and assessable as target lesions. Only the short axis measurement should be included in the sum of lesions in calculation of tumor response. Nodes that shrink to <1.0 cm short axis are considered normal.

11.23 All other lesions (or sites of disease), including small lesions (longest diameter <2.0 cm with chest X-ray or as <1.0 cm with CT scan, CT component of a PET/CT, or MRI) are considered non-measurable disease. Bone lesions leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CR or MRI), and cystic lesions are all non-measurable.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods: All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use spiral CT imaging for both pre- and post-treatment tumor assessments. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable imaging modalities for measurable disease: CT scan (conventional and spiral), MRI, chest x-ray, and physical examination.

- Conventional CT and MRI should be performed with cuts of 1.0 cm or less in slice thickness contiguously.
- Spiral CT must be performed using a 5 mm contiguous reconstruction algorithm. This specification applies to tumors of the chest, abdomen, and pelvis, while head and neck tumors and those of the extremities require specific procedures.

11.33 Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained 4 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see Section 11.44).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)
- New lesions on the basis of FDG-PET imaging can be identified according to the following:
  Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  No FDG-PET at baseline and a positive FDG-PET at follow-up:
  If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
  If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
  If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
  (A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue) on the attenuation corrected image.

11.4 Measurement of Effect

11.41 Target Lesions

All measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions representative of all involved organs should be identified as target lesions and recorded and measured at baseline. If the protocol specified studies are performed, and there are fewer than 5 lesions identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions. For any one organ, no more than 2 lesions need
to be measured. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

Baseline Sum of Diameters (BSD): A sum of the diameters [longest for non-nodal target lesions (see 11.21), short axis for target lymph nodes (see.11.22)] for all target lesions will be calculated and reported as the baseline sum of diameters. The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

Post-Baseline Sum of the Diameters (PBSD): A sum of the diameters [longest for non-nodal target lesions (see 11.21), short axis for target lymph nodes (see.11.22)] for all target lesions will be calculated and reported as the post-baseline sum of diameters. If the radiologist is able to provide an actual measure for the target lesion, that should be recorded, even if it is below 0.5 cm. If the target lesion is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 cm.

The minimum sum of the diameters (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All identified sites of disease must be followed on re-evaluation. Specifically, a change in objective status to either a PR or CR cannot be done without rechecking all identified sites (i.e., target and non-target lesions) of pre-existing disease.

11.432 Evaluation of Target Lesions

- Complete Response (CR): All of the following must be true:
  a) Disappearance of all non-nodal target lesions
  b) Each target lymph node must have reduction in short axis to < 1.0 cm.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter of the non-nodal target lesions and the short axis of the target lymph nodes taking as reference the BSD (Section 11.41)

- Progression (PD): At least one of the following must be true:

  a) At least one new malignant lesion or a lymph node whose short axis has increased to > 1.5 cm.
  b) At least a 20% increase in the sum of diameters of target lesions taking as reference the MSD. In addition, the sum must also demonstrate an absolute increase of at least 0.5 cm.
  c) See Section 11.33 for details in regards to the requirements for PD via FDG-PET imaging.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD.

11.433 Evaluation of Non-Target Lesions

- Complete Response (CR): All of the following must be true:
  a) Disappearance of all non-nodal non-target lesions
  b) Each non-target lymph node must have reduction in short axis to < 1.0 cm.

- Stable Disease (SD): Persistence of one or more non-target lesions

- Progression (PD): At least one of the following must be true:
  a) At least one new malignant lesion
  b) Unequivocal progression of existing non-target lesions. (Note: Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.)
  c) See Section 11.33 for details in regards to the requirements for PD via FDG-PET imaging.

NOTE: Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician will prevail, and the progression status will be confirmed at a later time by the study chair or a review panel.

11.44 Overall objective status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, non-target lesions, and new disease as defined in the following table.

Target Lesions	Non-Target Lesions	New Lesions	Overall Objective Status
CR	CR	No	CR
CR	SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

11.45 Residual Disease: In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

11.46 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

11.5 Response and Disease Progression

Formal statistical definitions of analysis variables involving response and disease progression are contained in Section 13.0.

12. DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.11 Method

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP web site (http://ctep.cancer.gov/reporting/cdus.html).

12.12 Responsibility for Submissions

Study participants are responsible for submitting CDUS data and/or data forms to the CTSU Data Operations Center quarterly by April 1, July 1, October 1 and January 1 to allow time for CTSU compilation, Principal Investigator review, and timely submission to CTEP (see Section 12.11.).

The CTSU Data Operations Center is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.2 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix B.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required. CTSU Operations will facilitate this process via email broadcasts and web postings.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded to the CTSU Regulatory Office in Philadelphia for entry in the Regulatory Support System (RSS) and transmission to CTEP.

12.3 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

The agent bevacizumab and temsirolimus, supplied by CTEP, DCTD, NCI, used in this protocol is provided to the NCI under a Collaborative Agreement (CTA-Clinical Trials Agreement) between the Pharmaceutical Company(ies) [hereinafter referred to as "Collaborator"] and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the Intellectual Property Option to Collaborator contained within the terms of award, apply to the use of Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient participating on the study or patient's family member, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall

be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data".):

a. NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and

other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract, and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Suite 7111
Bethesda, MD 20892
FAX 301-402-1584
E-mail: anshers@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Overview

This is a study in multiple tumor types treated with the combination of temsirolimus and bevacizumab. The five tumor types are of endometrium, ovary, hepatocellular, islet cell and carcinoid. The phase II trial is designed to assess treatment efficacy in terms of both tumor response and 6-month progression free survival. A modified two-stage Simon design[94] with fixed sample size is adopted for each of the five tumor groups respectively. This design will permit early stopping of the trial if there is strong evidence that the study regimen is inactive.

13.11 Primary Endpoints

The primary endpoint of this trial is treatment efficacy evaulated using both the tumor response rate and the 6-month progression free survival rate. Tumor response rate is the proportion of confirmed tumor responses. RECIST criteria will be used for response assessments. A confirmed tumor response is defined to be either a CR or PR noted as the objective status on 2 consecutive evaluations at least 8 weeks apart. The tumor response rate is defined as the total number of efficacy-evaluable patients who achieved a complete or partial response according to the RECIST criteria divided by the total number of efficacy-evaluable patients enrolled on study. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

The 6-month progression free survival rate is the proportion of efficacy-evaluable patients progression-free 6 months from registration. The 6-month progression-free rate is defined as the total number of efficacy-evaluable patients on study without documentation of disease progression 6 months from registration divided by the total number of efficacy-

evaluable patients enrolled on study. Patients who died without documentation of progression will be considered to have progressed on the date of their death. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for 6-month progression-free survival.

13.12 Sample Size

A maximum of 275 patients will be accrued to this trial if sufficient successes occur in all tumor types to be studied. The minimum number of patients to be accrued if there is insufficient activity to go to the second stage in any tumor type is 138. These estimates include an allowance for an extra 10% of patients to replace those deemed not evaluable due to ineligibility, major treatment violation, or cancellation.

Specifically, we will accrue a maximum of 55 patients [25 (Stage 1) + 25 (Stage 2) + 5 (10% over accrual)] for patients from each tumor group.

The maximum sample size will be increased to 299 patients after the addition of 24 [21 plus 3 (10% over accrual)] islet cell cancer who will receive single-agent bevacizumab.

13.13 Accrual Time and Study Duration

Based on accrual history in these diseases at each of the N01 participating consortia, we anticipate accruing approximately 25 eligible patients (ie, 5 –endometrial cancer, 6 –ovarian cancer, 5 – hepatocellular carcinoma, 4 – islet cell, 5 – carcinoid) per month. This estimate accounts for 10% over accrual for patients declared not evaluable due to ineligibility, major treatment violation, or cancellation. We expect the trial to be completed in 17 months for endometrial cancer, 16 months for ovarian cancer, 17 months for hepatocellular carcinoma, 20 months for islet cell cancer, 17 months for carcinoid, which includes a 6-month temporary suspension once the initial stage of accrual is met and to allow patients to become evaluable for the primary endpoint. Accrual will be temporarily closed during the interim analysis only if patient accrual is rapid. However, temporarily closure for interim analysis for one tumor group should not affect the status of other tumor groups. The final analyses will begin approximately 17 months, 16 months, 17 months, 20 months, 17 months after accrual is opened to endometrial cancer, ovarian cancer, hepaocellular carcinoma, islet cell and carcinoid patients respectively.

The accrual rate of islet cell patients treated with single agent bevacizumab is estimated to be 3 per month. We expect the accrual and analysis to be completed in 8 months for this additional cohort of islet cell cancer.

13.2 Statistical Design

A two-stage phase II clinical trial design has been chosen for each of the tumor groups such that under the assumption that tumor response and 6-month progression free survival are uncorrelated, there will be approximately 87%--92% chance of detecting the target tumor response rate or the target 6-month progression free survival rate at a 10% significance level. Instead of pursuing the optimal or minmax sample size as in Simon optimal design[94], a fixed sample size of 50 and a first stage sample size of 25 are used to assess efficacy for each of the five tumor groups.

13.21a Endometrial Cancer Decision Rule

A response rate of 25% and median progression free survival of 6 months were observed in the single agent activity of temsirolimus in patients who have recurrent or metastatic endometrial cancer [44]. To evaluate endometrial cancer, the largest response rate where the proposed treatment regimen would be considered ineffective in this population is 25%, and the smallest that would warrant further subsequent studies is 45%; the largest 6-month progression free survival rate where the proposed treatment regimen would be considered ineffective in this population is 50%, and the smallest that would warrant further subsequent studies is 70%. The following modified two-stage Simon design (Simon, 1989) uses 25 or 50 patients to test the null hypothesis that the true tumor response rate in the given patient population is at most 25% **AND** the true 6-month progression-free survival rate is at most 50%.

STAGE 1: Enter 25 patients into this study. If more than 7 of the first 25 evaluable patients enrolled achieved a confirmed tumor response during the first 6 cycles of treatment **OR** more than 13 of the first 25 evaluable patients enrolled were progression free at 6 months then enrollment would continue to the second stage. If not, patient accrual will be terminated and the regimen would be considered inactive in this patient population.

STAGE 2: Enter an additional 25 patients into this study. If at least 18 of the first 50 evaluable patients enrolled achieve a confirmed tumor response **OR** at least 31 of the first 50 evaluable patients enrolled are progression free at 6 months, consideration would be given to recommending this treatment for further testing in this patient population.

13.21b Ovarian Cancer Decision Rule

The Gynecology Oncology Group reported a single agent trial of bevacizumab in persistent or recurrent ovarian cancer [74], where the response rate was 21% and 40.3% patients were progression-free for at least 6 months. To evaluate ovarian cancer, the largest response rate where the proposed treatment regimen would be considered ineffective in this population is 20%, and the smallest that would warrant further subsequent studies is 40%; the largest 6-month progression free survival rate where the proposed treatment

regimen would be considered ineffective in this population is 40%, and the smallest that would warrant further subsequent studies is 60%. The following modified two-stage Simon design[94] uses 25 or 50 patients to test the null hypothesis that the true tumor response rate in the given patient population is at most 20% **AND** the true 6-month progression-free survival rate is at most 40%.

STAGE 1: Enter 25 patients into this study. If more than 6 of the first 25 evaluable patients enrolled achieved a confirmed tumor response during the first 6 cycles of treatment **OR** more than 10 of the first 25 evaluable patients enrolled were progression free at 6 months then enrollment would continue to the second stage. If not, patient accrual will be terminated and the regimen would be considered inactive in this patient population.

STAGE 2: Enter an additional 25 patients into this study. If at least 15 of the first 50 evaluable patients enrolled achieve a confirmed tumor response **OR** at least 26 of the first 50 evaluable patients enrolled are progression free at 6 months, consideration would be given to recommending this treatment for further testing in this patient population.

13.21c Hepatocellular Carcinoma Decision Rule

A single arm phase II trial of bevacizumab[88]reported an objective response rate 13% and 65% patients were progression-free at 6 months. Similarly, to evaluate hepatocellular carcinoma, the largest response rate where the proposed treatment regimen would be considered ineffective in this population is 10%, and the smallest that would warrant further subsequent studies is 25%; the largest 6-month progression free survival where the proposed treatment regimen would be considered ineffective in this population is 65%, and the smallest that would warrant further subsequent studies is 85%. The following modified two-stage Simon design[94] uses 25 or 50 patients to test the null hypothesis that the true tumor response rate in the given patient population is at most 10% **AND** the true 6-month progression-free survival rate is at most 65%.

STAGE 1: Enter 25 patients into this study. If more than 2 of the first 25 evaluable patients enrolled achieved a confirmed tumor response during the first 6 cycles of treatment **OR** more than 18 of the first 25 evaluable patients enrolled were progression free at 6 months then enrollment would continue to the second stage. If not, patient accrual will be terminated and the regimen would be considered inactive in this patient population.

STAGE 2: Enter an additional 25 patients into this study. If at least 9 of the first 50 evaluable patients enrolled achieve a confirmed tumor response **OR** at least 39 of the first 50 evaluable patients enrolled are progression free at 6 months, consideration would be given to recommending this treatment for further testing in this patient population.

13.21d Islet Cell Cancer Decision Rule

A multi-center trial of temsirolimus was conducted in metastatic neuroendocrine tumors with an observed response rate of 7% and an median time-to progression of 10.6 months[92]. Assuming a constant hazard rate, the median time-to progression of 10.6 months can be converted to an approximately 67.5% progression free rate at 6 months. Since some patients may be died from other causes than islet cell cancer, we estimate that progression free survival at 6 months would be a little lower at 60%. To evaluate islet cell cancer, the largest response rate where the proposed treatment regimen would be considered ineffective in this population is 5%, and the smallest that would warrant further subsequent studies is 20%; the largest 6-month progression free survival rate where the proposed treatment regimen would be considered ineffective in this population is 60%, and the smallest that would warrant further subsequent studies is 80%. The following modified two-stage Simon design[94]uses 25 or 50 patients to test the null hypothesis that the true tumor response rate in the given patient population is at most 5% **AND** the true 6-month progression-free survival rate is at most 60%. Due to the slow progression of islet cell cancer, we will not temporarily close to patient accrual after Stage 1 unless patient accrual is very rapid or severe toxicity occurred.

STAGE 1: Enter 25 patients into this study. If more than 2 of the first 25 evaluable patients enrolled achieved a confirmed tumor response during the first 6 cycles of treatment **OR** more than 15 of the first 25 evaluable patients enrolled were progression free at 6 months then enrollment would continue to the second stage. If not, patient accrual will be terminated and the regimen would be considered inactive in this patient population.

STAGE 2: Enter an additional 25 patients into this study. If at least 6 of the first 50 evaluable patients enrolled achieve a confirmed tumor response **OR** at least 36 of the first 50 evaluable patients enrolled are progression free at 6 months, consideration would be given to recommending this treatment for further testing in this patient population.

13.21e Carcinoid Decision Rule

A phase II clinical trial using bevacizumab was conducted in patients with carcinoid tumors showed promising antitumor activity [91] of a 18% partial response rate. A phase II study of temsirolimus in 37 patients with advanced progressive neuroendocrine carcinoma [92] reported a partial response rate of 5% and 6-month progression free survival rate of 45% noted in carcinoid tumor patients. To evaluate carcinoid, the largest response rate where the proposed treatment regimen would be considered ineffective in this population is 15%, and the smallest that would warrant further subsequent studies is 35%; the largest 6-month progression free survival rate where the proposed treatment regimen would be considered ineffective in this population is 45%, and the smallest that would warrant further subsequent studies is 65%. The following modified two-stage Simon design[94]uses 25 or 50 patients to test the null hypothesis that the true tumor response rate in the given patient population is at most 15% **AND** the true 6-month progression-free survival rate is at most 45%. Due to the slow progression of Carcinoid, we will not temporarily close to patient accrual after Stage 1 unless patient accrual is very rapid or severe toxicity occurred.

STAGE 1: Enter 25 patients into this study. If more than 5 of the first 25 evaluable **patients (evaluable patients are defined as patients who have received any dose of study drug on this trial)** enrolled achieved a confirmed tumor response during the first 6 cycles of treatment **OR** more than 12 of the first 25 evaluable patients enrolled were progression free at 6 months then enrollment would continue to the second stage. If not, patient accrual will be terminated and the regimen would be considered inactive in this patient population.

STAGE 2: Enter an additional 25 patients into this study. If at least 12 of the first 50 evaluable patients enrolled achieve a confirmed tumor response **OR** at least 28 of the first 50 evaluable patients enrolled are progression free at 6 months, consideration would be given to recommending this treatment for further testing in this patient population.

13.21 f Islet Cell Cancer Single Agent Bevacizumab Cohort Decision Rule

The efficacy of single agent Bevacizumab will be compared against Sunitinib, an approved anti-VEGF therapy. Tumor response will be considered as the sole primary endpoint for this single agent Bevacizumab cohort of ICC patients. A phase II clinical trial of Sunitinib reported a median PFS of 7.7 months and response rates of 16% (Kulke et al JCO, 2008). A randomized phase III clinical trial of Sunitinib vs placebo reported a median PFS of 11.4 months (71% PFS at 6 month) and response rate of 9%. (Raymond et al NEJM, 2011). To evaluate the efficacy of single agent Bevacizumab, we have modified the null and alternative hypothese to reflect that fact we are testing the

superiority of Bevacizumab over Sunitinib. The largest response rate where the proposed treatment regimen would be considered ineffective in this population is 10%, and the smallest that would warrant further subsequent studies is 30%. The single-stage design uses 21 patients to test the null hypothesis that the true tumor response rate in the given patient population is at most 10%. We will reject the null hypothesis if we have at least 7 confirmed responses.

13.22 Power and Significance Level

Assuming that the number of confirmed tumor responses and the number of 6-month progression-free survivors are binomially distributed and uncorrelated, the significance level is at most 10% and the probability of declaring that this regimen warrants further studies (i.e. statistical power) under various success proportions and the probability of stopping accrual after the first stage can be tabulated as a function of the true success proportion as shown in the following tables.

Endometrial : probability of stopping accrual at stage 1:

		True 6-month Progression-Free Survival Rate				
		50%	55%	60%	65%	70%
True Tumor Response Rate	25%	0.479	0.328	0.194	0.091	0.033
	30%	0.333	0.233	0.138	0.096	0.022
	35%	0.201	0.141	0.081	0.038	0.014
	40%	0.099	0.071	0.041	0.019	0.007
	45%	0.041	0.030	0.017	0.008	0.003

Endometrial Cancer: probability of declaring that the regimen warrents further studies:

		True 6-month Progression-Free Survival Rate				
		50%	55%	60%	65%	70%
True Tumor Response Rate	25%	0.099	0.224	0.451	0.714	0.901
	30%	0.237	0.338	0.538	0.758	0.915
	35%	0.481	0.548	0.681	0.836	0.941
	40%	0.732	0.768	0.831	0.915	0.970
	45%	0.895	0.911	0.938	0.967	0.988

Ovarian Cancer: probability of stopping accrual at stage 1:

		True 6-month Progression-Free Survival Rate				
		50%	55%	60%	65%	70%
True Tumor Response Rate	20%	0.514	0.351	0.207	0.097	0.034
	25%	0.368	0.258	0.152	0.069	0.024
	30%	0.223	0.155	0.092	0.042	0.015
	35%	0.116	0.078	0.047	0.022	0.008
	40%	0.047	0.034	0.020	0.009	0.003

Ovarian Cancer: probability of declaring that the regimen warrents further studies:

		True 6-month Progression-Free Survival Rate				
		50%	55%	60%	65%	70%
True Tumor Response Rate	20%	0.097	0.221	0.450	0.714	0.903
	25%	0.255	0.355	0.547	0.764	0.919
	30%	0.509	0.573	0.700	0.845	0.948
	35%	0.753	0.785	0.849	0.921	0.974
	40%	0.905	0.917	0.942	0.970	0.989

Hepatocellular Carcinoma: probability of stopping accrual at stage 1:

		True 6-month Progression-Free Survival Rate				
		65%	70%	75%	80%	85%
True Tumor Response Rate	10%	0.444	0.353	0.235	0.119	0.037
	15%	0.210	0.168	0.111	0.057	0.018
	20%	0.080	0.067	0.043	0.020	0.007
	25%	0.027	0.021	0.014	0.007	0.002

Hepatocellular Carcinoma: probability of declaring that the regimen warrents further studies:

		True 6-month Progression-Free Survival Rate				
		65%	70%	75%	80%	85%
True Tumor Response Rate	10%	0.082	0.164	0.368	0.663	0.904
	15%	0.340	0.401	0.544	0.758	0.929
	20%	0.687	0.715	0.784	0.882	0.966
	25%	0.899	0.909	0.930	0.964	0.989

Islet Cell: probability of stopping accrual at stage 1:

		True 6-month Progression-Free Survival Rate				
		60%	65%	70%	75%	80%
True Tumor Response Rate	5%	0.505	0.320	0.166	0.062	0.015
	10%	0.307	0.200	0.102	0.038	0.009
	15%	0.143	0.096	0.048	0.018	0.004
	20%	0.056	0.037	0.018	0.007	0.002

Islet Cell: probability of declaring that the regimen warrents further studies:

		True 6-month Progression-Free Survival Rate				
		60%	65%	70%	75%	80%
True Tumor Response Rate	5%	0.080	0.202	0.454	0.743	0.933
	10%	0.333	0.425	0.606	0.814	0.953
	15%	0.685	0.731	0.814	0.912	0.977
	20%	0.889	0.903	0.936	0.969	0.992

Carcinoid: probability of stopping accrual at stage 1:

		True 6-month Progression-Free Survival Rate				
		45%	50%	55%	60%	65%
Tru e Tu mo	15%	0.582	0.420	0.259	0.129	0.049
	20%	0.427	0.305	0.192	0.092	0.038

	25%	0.269	0.191	0.118	0.059	0.024
	30%	0.136	0.096	0.058	0.029	0.011
	35%	0.058	0.040	0.024	0.013	0.006

Carcinoid: probability of declaring that the regimen warrents further studies:

		True 6-month Progression-Free Survival Rate				
		45%	50%	55%	60%	65%
True Tumor Response Rate	15%	0.111	0.249	0.483	0.728	0.902
	20%	0.271	0.383	0.577	0.779	0.920
	25%	0.535	0.607	0.732	0.862	0.949
	30%	0.771	0.808	0.866	0.931	0.975
	35%	0.908	0.922	0.948	0.973	0.991

In this design, we assume that tumor response and 6-month progression-free survival are uncorrelated. Through investigating past NCCTG phase II metastatic breast cancer trials (N0032, N0234, and 98-32-53), tumor response and 6-month progression-free survival may have significantly non-zero positive correlation of roughly 0.50 in some settings. Through simulation with various distributional assumptions and correlation levels, the significance level under the assumption of uncorrelated binary endpoints appears to be conservative (i.e. worst-case scenario) and the power under alternative hypothesis of tumor response rate and 6-month progression free survival rate appears greater than the specified level regardless of the level of correlation.

For islet cell patient cohort treated with single agent bevacizumab, we have set the significance level around 10% and still maintain the the probability of declaring that this regimen warrants further studies (i.e. statistical power) above 80%. The sample size of 21 evaluable patients will be sufficient for testing Bevacizumab only based on the one-sided exact test of single proportion of 10% vs. 30%.

13.23 Other Considerations

Adverse events, duration of response, overall survival, and the pace of accrual as well as other scientific discoveries or changes in standard of care will be taken into account in any decision to terminate this study earlier than designed.

13.3 Analysis Plan

The following analyses will be conducted for each of the five tumor groups respectively except for a possible exploratory meta analysis at the very end of the study. However, the final conclusion of the study will be based on each of the separate analysis of the tumor groups.

13.31 Primary Endpoint:
All patients meeting the eligibility criteria who have signed a consent form and begun treatment will be considered evaluable for estimation of

the success probability. Those who die within 6 months will be considered to have had disease progression unless documented evidence clearly indicates no progression has occurred.
In the event that such evidence is obtained, or in the case of major treatment violation, the patients' response data will be considered censored at the date the patient was withdrawn from treatment.

The true tumor response rate will be estimated by proportion of efficacy-evaluable patients who achieved a confirmed CR or PR by the RECIST criteria. A 95% confidence interval for the true response rate will be constructed using the Duffy-Santner approach[95].

The true 6-month progression-free survival rate will be estimated by the proportion of efficacy-evaluable patients on study without documentation of disease progression 6 months from registration. A 95% confidence interval for the true response rate will be constructed using the Duffy-Santner approach[95]. However, Kaplan-Meier methodology will be used to estimate the final success proportion (i.e. progression free at 6 months with a 95% confidence interval) if there are censored patients.

13.32 Definitions and Analyses of Secondary Endpoints:

13.321 Overall survival

Survival time will be defined as the time from registration to death. Time to event distributions will be estimated using the Kaplan-Meier method[96].

13.322 Duration of response

Duration of response is defined for all evaluable patients who have achieved an objective response as the date at which the patient's objective status is first noted to be either a CR or PR to the date progression is documented. Median duration of response and the confidence interval for the median duration will be computed.

13.323 Time to disease progression

Time to progression is defined as the time from registration to disease progression. Patients who died without documentation of progression will be considered to have progressed on the date of their death. If a patient starts treatment and fails to return for evaluation, that patient will be censored for progression of disease at day one post-registration.

13.324 Time to treatment failure

Time to treatment failure is defined as the time from study entry to the date patients end treatment. These analyses will include those patients who go off treatment in the first cycle as well as those included in the efficacy analyses. Time to treatment failure will be evaluated using the method of Kaplan-Meier.

13.325 Translational endpoints

Various correlative assays and markers may be explored in an independent study as indicated under laboroatory correlates. Thus we cannot propose a method of analysis for any data generated from samples collected on this trial at this time.

13.33 Adverse events

All eligible patients that have initiated treatment will be considered evaluable for adverse event analyses. The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine adverse event patterns. As per NCI CTCAE Version 3.0, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and classified as either "unrelated or unlikely to be related" to study treatment in the event of an actual relationship developing. Adverse events and toxicities will be evaluated using all patients who have received any study treatment as well as summarizing those who have been included in the efficacy analyses.

13.34 Over Accrual

If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals as though they were accrued in the final stage.

13.35 Monitoring

The principal investigator(s) and the study statistician will review the study periodically (at least twice a year) to identify accrual, adverse events, and any endpoint problems that might be developing. This study will also be monitored by the Mayo Clinic Cancer Center Data and Safety Monitoring Board (DSMB) at least semiannually, or more frequently as warranted.

13.36 Adverse Events Stopping Rule

Overall, if 5 or more of the first 25 patients (or 20% of all patients after 25 are accrued) experience grade 4/5 non-hematologic adverse events that are probably, possibly, or definitely related to study treatment, accrual to the study will be suspended to allow for investigation. For the single-agent bevacizumab cohort for islet cell patients, a separate but similar adverse events stopping rule will be applied. If 2 or more of the first 10 patients or 20% of all patients after 10 patients are accrued experience grade 4/5 non-hematologic adverse events that are probably, possibly, or definitely related to study treatment, accrual to the study will be suspended to allow for investigation. After consideration by the study team (study chair[s], statistician, etc.) and the primary data safety monitoring board, a decision will be made as to whether accrual can be resumed. In addition, all adverse event patterns will be monitored by an independent Mayo Clinic Data Safety Monitoring Board on a bi-annual basis.

13.37 Meta Analysis

Treating five tumor groups with the combination of temsirolimus and bevacizumab under one protocol will provide a standardized platform for carrying out a possible exploratory meta analyses. Pooling patients of different tumor data in the meta analyses will increase precision of estimation and allow borrowing strength across tumor groups. We will explore such a meta analysis when all data are mature across all five patient tumor groups.

13.4 Inclusion of Women and Minorities

13.41 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

13.42 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

13.43 The geographical region served by N01 consortia, has a population mirrors of general U.S. population.
This includes approximately 25% minorities. Based on prior NCCTG studies involving similar disease sites, we expect about 25% of patients will be classified as minorities by race and about 100% of patients will be women for Endometrial and Ovary cancer patients, 50% for Carcinoid, Islet Cell and Hepatoma. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race for All Phase 2 and 3 Studies

Ethnic Category	Sex/Gender			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	19	9	0	28
Not Hispanic or Latino	188	83	0	271
Ethnic Category: Total of all subjects*	207	92	0	**299***
Racial Category				
American Indian or Alaskan Native	2	1	0	3
Asian	6	3	0	9
Black or African American	19	8	0	27
Native Hawaiian or other Pacific Islander	2	1	0	3
White	178	79	0	257
Racial Category: Total of all subjects*	207	92	0	**299***

These totals must agree. Enter actual estimates (not percentages**)*

Ethnic Categories: **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories: **American Indian or Alaska Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14. Descriptive Factors

14.1 Islet Cell Cancer Patients Only
Functioning (hormone producing) vs. non-functioning (non-hormone producing)

14.2 Carcinoid Cancer Patients Only
Functioning (hormone producing) vs. non-functioning (non-hormone producing)

14.3 Ovarian Cancer Patients Only
Platinum-sensitive vs. platinum resistant (defined as recurrence within six months of completing initial platinum-based chemotherapy).

14.4 Hepatocellular Carcinoma Patients Only
Chronic liver disease: Yes vs. No
If yes, specify from the following: Hepatitis B vs. Hepatitis C vs. Hepatits B & C vs. Alcoholic cirrhosis vs. Alcoholic cirrhosis + Hepatitis B vs. Alcoholic cirrhosis + Hepatitis C vs. Alcoholic cirrhosis + Hepatitis B & C vs. Hematochromatosis vs. Cirrhosis NOS vs. Other, (specify).

14.5 Carcinoid and Islet Cell Cancer Patients Only
Did patient have progressive disease based on RESCIST in preceding 6 months: Yes vs No vs N/A.

15. PATHOLOGY CONSIDERATIONS

Histologic or cytologic confirmation of disease will be the responsibility of each center independently without central review. Copies of pathology reports are to be sent to the CTSU Data Operations within two weeks of study entry (see Section 16.3).

16. DATA SUBMISSION TO DATA OPERATIONS CENTER (CTSU)

Clinical Data Submission via Remote Data Capture

All participating sites will submit patient data via the CTSU's Remote Data Capture (RDC) system. The CTSU RDC system allows sites to enter patient data into an Oracle Clinical ® (OC) database over a secure Internet connection. The RDC system also allows for data correction at the point of entry, and is used to communicate and resolve issues relating to discrepant data. The Remote Data Capture (RDC) Production Application is for those individuals who have completed their RDC training and are ready to enter actual patient data into the system. If you have not yet received training in the RDC system, please go to the CTSU Members' side of the website (https://www.ctsu.org) and click on the "Clinical Data" tab at the top of your screen, followed by the "Remote Data Capture" link on the left-hand side of your screen. Select the "Training" tab to request a training account.

Clinical Report Submission via Fax

In addition to submitting patient data electronically via the RDC system, sites may be required to submit faxed clinical reports to CTSU. Clinical reports (e.g. operative and pathology reports) must be faxed to the CTSU Data Operations Center accompanied by a properly completed study-specific CTSU Data Transmittal Form. (Data submitted improperly or without a completed CTSU Data Transmittal Form will not be processed. Site will receive e-mail notification for any unsuccessful data receipt, including a data resubmission memo which will provide details and instructions for re-submission). Include the Patient ID and protocol number on all pages of the report and redact the patient's name. **CTSU fax number is: 1-301-545-0406.**

Data Submission Questions

The CTSU help desk is available to answer questions regarding data submission at 1-888-823-5923 or by email at ctsucontact@westat.com. Hours are between 9:00 A.M. and 5:30 P.M. Eastern Time, Monday through Friday (excluding holidays).

16.1 Schedule of Data Submission

Data is to be submitted ≤ 2 weeks following each evaluation of the patient and according to the scheduled in Section 16.3

After the patient discontinues treatment, follow–up will continue as specified in the following section(s):

16.2 Event Monitoring

Follow-up data will be collected and entered via the remote data entry system according to the schedule in Section 16.3. If patient is still alive after 3 years have elapsed from on-study date, no further follow-up is required by this protocol.

16.21 If a patient does not receive treatment (and is classified as a cancel), it is not necessary to provide follow-up information. On-study material, End of active treatment/cancel notification form and Off Study Form are to be submitted. No further follow-up information is necessary.

16.22 If a patient declared to be ineligible, all on-study and study treatment materials are to be submitted. The patient will enter the event monitoring phase of this study and will be followed for a maximum of 3 years or until death.

16.3 Data Entry/Submission Timetable

Forms/Other	Active Monitoring Phase (Compliance with Test Schedule)			Event-Monitoring Phase[2] (Completion of Active Monitoring Phase)				At Each Occurrence		
	Initial Material	Subsequent material								
	£2 weeks after registration	At each evaluation	At end of treatment	q. 3 months until PD[2]	At PD[2]	After PD q. 6 mos.[2]	Death	All Grade 4/5 AEs All Hospitalizations During Treatment Secondary AML/MDS	New Primary	Late Adverse Event
On-Study Form	X									
Baseline Adverse Events Form	X									
Measurement Form	X	X[4]	X[4]							
Paths & Op Reports[1]	X									
Biochemical Laboratory Form	X[7]	X[7]			X[8]					
Event Monitoring Form			X	X[4]	X[4]	X	X		X	X
Evaluation/Treatment Form		X	X							
Nadir/Adverse Event Form		X	X							
Blood Specimen Submission Form	X									
Tissue Specimen Submission form (Section 9.1)	X									
Notification Form, Grade 4/5								X		
End of Active Treatment/Cancel Notification Form	X[5]		X							
Off Study Form	X[6]						X[6]			
AE Reporting per Section 7.0								X[3]	X	
CTEP Report Variables Form	X									

1. Submit copy of pathology reports via fax or mail to the CTSU Data Operations via fax (1-301-545-0406) and a pathology report must be submitted along with tissue submission form when the samples are sent to Mayo Clinic.
2. If a patient is still alive 3 years after registration, no further follow-up is required.
3. Reminder: Adverse events that necessitate expedited reporting are also to be reported via the routine clinical data (i.e. Nadir/Adverse Event Form, etc.) submitted with each evaluation.

4. Submit copy of documentation of response, recurrence, or progression to the CTSU Data Operations via fax (1-301-545-0406).
5. Submit if withdrawal/refusal prior to beginning protocol therapy occurs.
6. Off study form would be completed if patient is a cancel, still alive 3 years after registration, at the time of death, lost to follow-up or refused follow-up.
7. Submit only for the Carcinoid, Islet Cell, Hcc and Ovarian Cohorts only
8. Submit only for the HCC and Ovarian Cohorts at PD, withdrawal or removal.

17. GROUPING FACTOR

Disease Site: Endometrial vs. ovarian vs. hepatocellular vs. carcinoid vs. islet cell (combined therapy) vs. islet cell -single –agent bevacizumab**).**

18. FUNDING CONSIDERATIONS

18.1 Costs Charged to Patient

All routine clinical care. temsirolimus and Bevacizumab will be provided by the NCI. The patient or the patient's health plan/insurer will be responsible for charges associated with supplies and procedures necessary for administration of the study drug(s), as well as all other drugs or treatment given to help control adverse events as well as the cost of tests or exams to evaluate possible adverse events**.**

18.2 Tests to be Research Funded

The cost of the collection and shipment of samples will be requested from the TBD. P2C institutions are responsible for other local costs associated with research specimen collection, processing, and shipment.

18.3 Support from N01 P2C Contract

This study is supported by The Phase 2 Consortium (P2C) through its contract with the National Cancer Institute (N01 CM62205).

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APPENDIX A: ECOG PERFORMANCE STATUS

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.

- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX C: CHILD-PUGH CLASSIFICATION OF HEPATIC FUNCTIONAL RESERVE

Child-Turcotte-Pugh Scoring System

Parameter	1 Point	2 Points	3 Points	Score
INR*	<1.7	1.7 - 2.3	>2.3	
Prothrombin Time (PT)* (seconds over control)	<4	4-6	>6	
Albumin	>35 g/L, (> 3.5 g/dL)	28-35 g/L, (2.8-3.5 g/dL)	<28 g/L (< 2.8 g/L)	
Bilirubin	<34 µmol/L (<1.8 mg/dL)	34-50 µmol/L (1.8-2.6 mg/dL)	>50 µ/L (>2.6 mg/dL)	
Ascites	Absent	Slight Or controlled by diuretics	Moderate	
Encephalopathy	None	1-2	3-4	
Total Score (A=5-6; B=7-9; C=10-15)				

**For scoring purposes, both PT and INR are not required. Either test can be used for scoring but in the case that both tests are drawn, use the higher score of the 2.*
Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the esophagus for bleeding esophageal varices. Br J Surg 1973; 60:646-649

Clinical Stages of Hepatic Encephalopathy

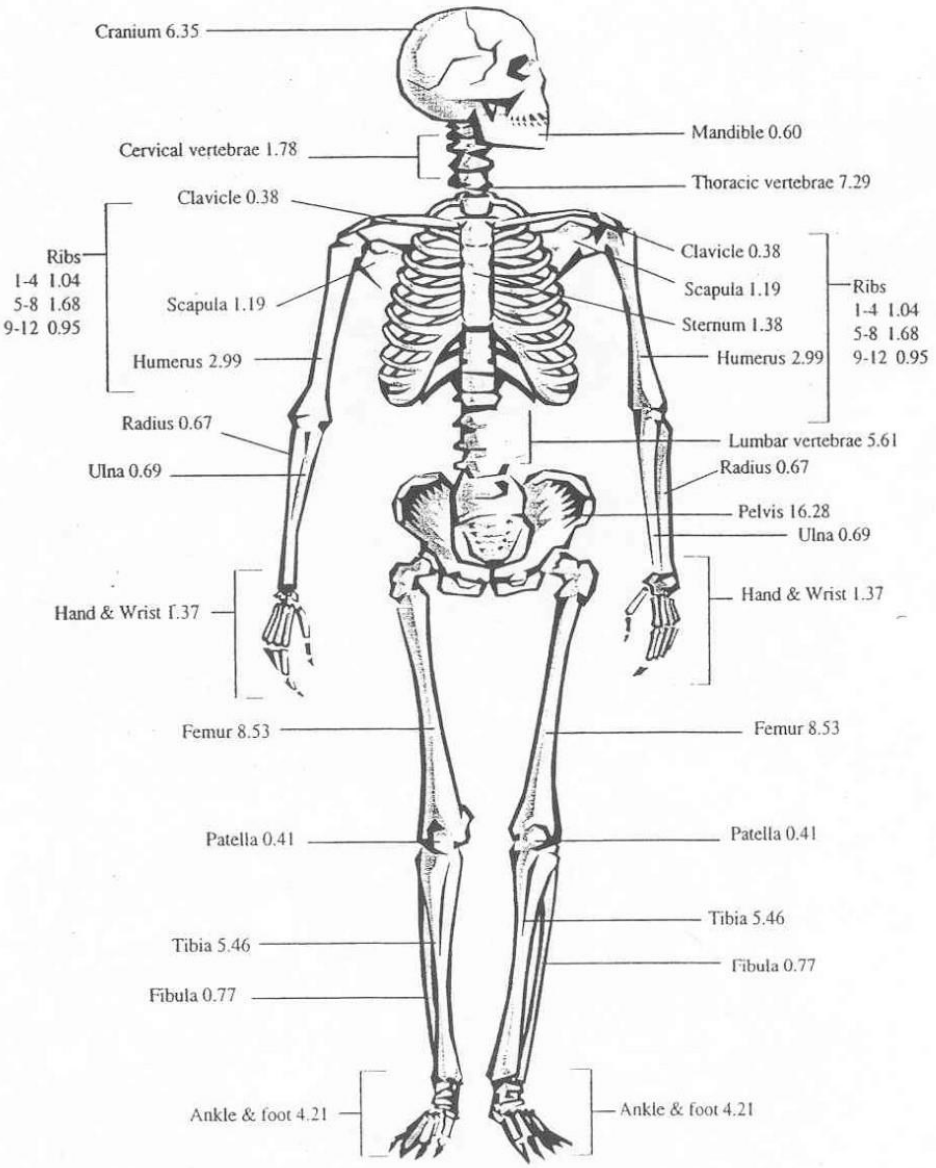
Stage	Mental State
0	Normal
1	Mild confusion, euphoria or depression, decreased attention, slowing of ability to perform mental tasks, irritability, disorder of sleep pattern.
2	Drowsiness, lethargy, gross deficits, inability to perform mental tasks, obvious personality changes, inappropriate behavior, intermittent disorientation (usually for time). Asterixis.
3	Somnolent but rousable, unable to perform mental tasks, disorientation with respect to time and/or place, marked confusion, amnesia, occasional fits of rage, speech present but incomprehensible. Asterixis.
4	Coma

APPENDIX D: KNOWN INHIBITORS AND INDUCERS OF CYP3A4

Inducers	
Carbamazepine Dexamethasone Ethosuximide Glucocorticoids Griseofulvin Nafcillin Nelfinavir Nevirapine Oxcarbazepine Phenobarbital Phenylbutazone	Phenytoin Primidone Progesterone Rifabutin Rifampin Rofecoxib (mild) St John's wort Sulfadimidine Sulfinpyrazone Troglitazone
Inhibitors	
Amiodarone Anastrozole Azithromycin Cannabinoids Cimetidine Clarithromycin Clotrimazole Cyclosporine Danazol Delavirdine Dexamethasone Diethyldithiocarbamate Diltiazem Dirithromycin Disulfiram Entacapone (high dose) Erythromycin Ethinyl estradiol Fluconazole (weak) Fluoxetine Fluvoxamine Gestodene Grapefruit juice Indinavir Isoniazid Itraconazole	Ketoconazole Metronidazole Mibefradil Miconazole (moderate) Nefazodone Nelfinavir Nevirapine Norfloxacin Norfluoxetine Omeprazole (weak) Oxiconazole Paroxetine (weak) Propoxyphene Quinidine Quinine Quinupristin and dalfopristin Ranitidine Ritonavir Saquinavir Sertindole Sertraline Troglitazone Troleandomycin Valproic acid (weak) Verapamil Zafirlukast Zileuton

APPENDIX E: PERCENT BONE MARROW

Percent Bone Marrow in the Adult Skeleton



Woodward HQ, Holodny E. A summary of the data of Mechanik on the distribution of human bone marrow. Phys Med Biol. 1960;5:57-59

APPENDIX F: NEW YORK HEART ASSOCIATION CLASSIFICATIONS

Clinical Evaluation of Functional Capacity of Patients
with Heart Disease in Relation to Ordinary Physical Activity

Class	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability to work**
I	None	None	None	Full time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, and any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

** At accustomed occupation or usual tasks.

Reference: Bruce, R. A.: Mod. Concepts Cardiovasc. Dis. 25:321, 1956. (Modified from New York Heart Association, 1953).

APPENDIX G: SPECIMEN SUMMARY

Collection Tube Description and /or additive (color of tube top	Volume to be collected per tube (number of tubes to be collected)	Blood product to be processed	Visit Description £7 Days Prior to Registration	Further Processing by BAP	Shipping Conditions
EDTA (purple)	7 mL (1)	Plasma, Buffy Coat [1]	X	No	Frozen

1. All specimens will be stored in BAP until further research is defined.