The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Phase III Prospective Randomized Comparison Trial of Depot Octreotide Plus Interferon Alpha-2b Versus Depot Octreotide Plus Bevacizumab in Advanced Carcinoid Patients: SWOG S0518

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Activated December 1, 2007

SWOG

PHASE III PROSPECTIVE RANDOMIZED COMPARISON OF DEPOT OCTREOTIDE PLUS INTERFERON ALPHA VERSUS DEPOT OCTREOTIDE PLUS BEVACIZUMAB (NSC #704865) IN ADVANCED, POOR PROGNOSIS CARCINOID PATIENTS

This trial is a collaborative effort with the American College of Radiology Imaging Network (ACRIN)
ACRIN Study Number 6680

NCT #00569127

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Supplied by the NCI:
Bevacizumab (NSC #704865, IND #113918)

Commercial:
Interferon Alpha-2b
Octreotide Acetate for injectable suspension

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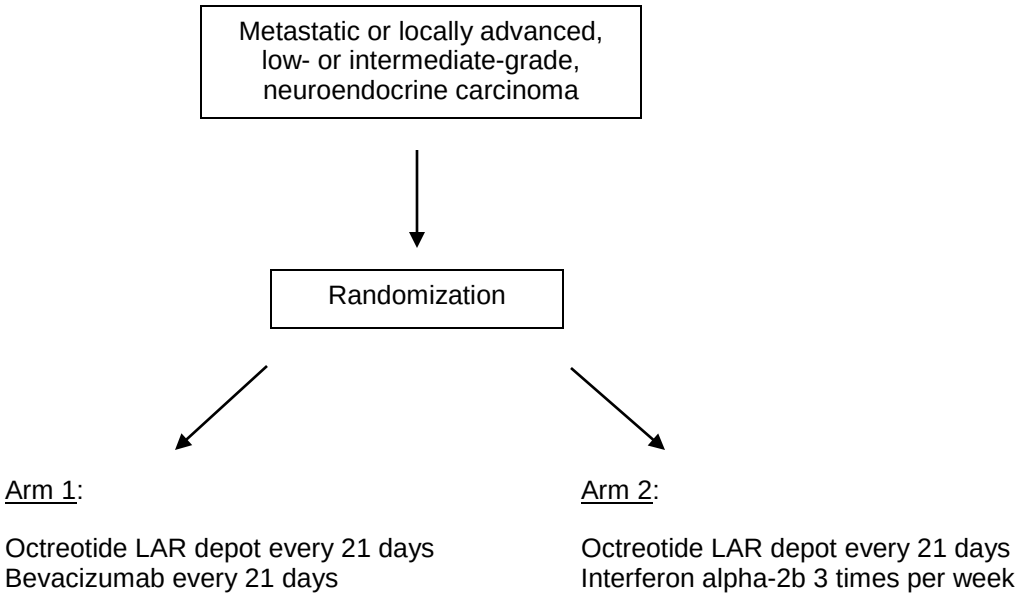
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	Su**bmit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA19103 Fax: 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org For more information, call the CTSU Help Desk at 888-823-5923 or the Regulatory Help Desk at 866-651-CTSU.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Preferred method: Fax: 800/892-4007 Do not submit study data or forms to CTSU Data operations. Do not copy CTSU on data submissions.
The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
<u>For patient eligibility questions</u> contact the SWOG Data Operations Center by phone or email: 206-652-2267 giquestion@crab.org **<u>For treatment or toxicity related questions contact the Study PI of the Coordinating Group.</u>**		
<u>For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail:</u> CTSU General Information Line: 888-823-5923 ctsucontact@westat.com All calls and correspondence will be triaged to the appropriate CTSU representative.		
<u>For detailed information on the regulatory and monitoring procedures for CTSU</u> sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website: https://www.ctsu.org > education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy		
The CTSU Web site is located at https://www.ctsu.org		

SCHEMA


Metastatic or locally advanced, low- or intermediate-grade, neuroendocrine carcinoma
Randomization
Arm 1:
Octreotide LAR depot every 21 days
Bevacizumab every 21 days
Arm 2:
Octreotide LAR depot every 21 days
Interferon alpha-2b 3 times per week

1.0 OBJECTIVES

1.1 Primary Objective

a. To compare central review-based progression-free survival in poor prognosis carcinoid patients treated with either depot octreotide plus bevacizumab, or depot octreotide plus interferon.

1.2 Other Objectives

a. To compare overall survival, time to treatment failure and traditionally reported progression-free survival in poor prognosis carcinoid patients treated with either depot octreotide plus bevacizumab, or depot octreotide plus interferon.

b. To compare objective response (confirmed and unconfirmed CR and PR) in poor prognosis carcinoid patients treated with either depot octreotide plus bevacizumab, or depot octreotide plus interferon.

c. To compare the toxicity profile of patients treated with these two regimens.

1.3 Translational Medicine Objectives

a. To assess the prognostic and predictive value of VEGF expression in relation to progression-free survival and treatment effect.

b. To compare response of 5HIAA, chromogranin A and neuronspecific enolase among patients with elevated levels at baseline between patients treated with octreotide plus interferon versus octreotide plus bevacizumab.

c. To assess and compare the prognostic and predictive value of the combination of In-111 pentetreotide somatostatin-receptor scintigraphy (SRS) and CT vs. CT in relation to progression-free survival (PFS).

d. To assess and compare the prognostic and predictive value of the combination of SRS and CT vs. CT in relation to overall survival (OS) and time to treatment failure (TTF).

2.0 BACKGROUND

Carcinoid

Carcinoid tumors originate from the neuroendocrine cells throughout the body and are capable of producing various peptides. Their clinical course is often indolent but can also be highly aggressive and resistant to therapy. Current treatments for bulky metastatic tumors have either low biologic activity, high unfavorable toxicity profile or both. Despite the many chemotherapy trials that have been conducted, no regimen has demonstrated conclusive clinical benefit. In the more recently reported Eastern Cooperative Oncology Group (ECOG) Phase III study of chemotherapy in carcinoid tumors (E1281), patients were randomly assigned to treatment with 5-FU plus doxorubicin or 5-FU plus streptozocin. *(1)* The median progression-free survival durations were disappointing. They were 4.5 months in the 5-FU plus doxorubicin arm and 5.3 months in the 5-FU plus streptozocin arm. Overall survival durations recorded in the trial were also suboptimal at 15 and 24 months respectively. There is no clear survival benefit for cytotoxic chemotherapy.

Other treatment options include vascular occlusion therapy. This method was developed to take advantage of the fact that the liver has a dual blood supply. Liver metastases depend largely on the hepatic artery for support. However, vascular occlusion therapy should be carried out only in

selected patients and only in a hospitalized setting since treatment-related toxic effects are common and can be severe. A constellation of transient symptoms and laboratory abnormalities, sometimes referred to as “postembolization syndrome,” occurs in most patients. These include abdominal pain, nausea, fever, fatigue, and elevation of liver enzymes. Carcinoid crises related to massive hormonal release can occur. Major complications (and even deaths) have been reported in clinical trials and include gastrointestinal bleeding, gastric and duodenal ulceration,

hepatic abscesses, ischemic necrosis of the gallbladder and small bowel, sepsis, renal failure, hepatorenal syndrome, portal vein thrombosis, arterial thrombosis, and arrhythmia. *(2)* Two cases of sclerosing cholangitis were reported in an early trial using bovine collagen fibers for embolization. Due to the unfavorable toxicity profile associated with hepatic artery embolization, it is currently only used in highly selected patients with disease limited to the liver.

At the current time, most patients with advanced carcinoid will die from the disease. Analyses of the SEER database showed the median survival of patients with metastatic carcinoid to vary by primary site. Among patients diagnosed between 1987 and 2001, median survival durations range from 8.1 months for hindgut primary (colorectal excluding appendix and cecum) to 56.7 months for small bowel primary (Table 1). *(3)*

Table 1. Survival duration associated with metastatic low grade neuroendocrine carcinoma by primary site

Primary site	Median survival (months)
Respiratory	13.1
Stomach	8.7
Pancreas	31.0
Small bowel	56.7
Cecum/appendix	41.9
Colorectal (not cecum or appendix)	8.1

While carcinoid tumors can be slow growing, patients with tumor growth, atypical histology (intermediate grade or moderately differentiated) carcinoid, and gastric or colorectal (not cecum or appendix) primaries have poor prognosis. Progression-free survival durations from recently reported trials are listed in Table 2.

Table 2. Progression-free survival duration in recently reported trials

Treatment (reference)	Median	Proportion progression-free
5-FU, doxorubicin *(1)*	4.5 months	
5-FU, streptozocin *(1)*	5.3 months	
Bortezomib *(4)*	3 months*	25% at 24-weeks*
Imatinib (unpublished data)	6 months	50% at 24-weeks
Gefitinib *(5)*		61% at 6-months
Octreotide, peg-interferon		68% at 18-weeks
Octreotide, bevacizumab	> 12 months	96% at 18-weeks
SU11248	42 weeks	

* Time to treatment failure

Basic fibroblast growth factor (bFGF), a stimulant of endothelial cell growths has been found to be expressed in both carcinoid tumor tissue and carcinoid cell line. Development of newer less toxic strategies based on the inhibition of tumor angiogenesis are underway.

Octreotide in carcinoid tumors

Octreotide is a peptide approved for the management of carcinoid syndrome. While it has significant activity in inhibiting hormonal output from carcinoid tumors, it has not resulted in objective tumor responses. Data were pooled from trials using octreotide for which the number ofpatients with measurable disease and the number of patients with objective tumor responses were documented. Among a total of 182 patients assessable for tumor response, only 3 partial responses (2%) were documented.

Somatostatin analogues have been reported to have antiangiogenic properties. *(6-16)* The described cytostatic activity of somatostatin analogues on carcinoid tumors may be mediated through its anti-angiogenic effects. Decreases in plasma VEGF and IGF-1 have been observed

in one colon cancer study and another non-endocrine tumors study. *(6,9)* In a human xenograft model of hindgut neuroendocrine tumor, treatment with somatostatin analogue resulted in decreased plasma VEGF and bFGF as well as micro vessel density. *(13)* In addition, octreotide has also been described to inhibit endothelial proliferation through somatostatin receptors present on endothelial cells. *(17)*

Interferon in carcinoid tumors

Interferon alpha has also been widely studied in this disease. Pooling the data from patients with carcinoid involved in these trials, only 37 (12%) of 309 had objective tumor responses. There is evidence of synergy for biologic agents in carcinoid. Three trials have studied the combination of concurrent octreotide and interferon alpha. Biochemical response rates of 72-77% were reported. In one trial, 9 of 17 patients who had biochemical responses to this combination had previously failed both octreotide and interferon alpha as single agents.

Interferon alpha has been described to have antiangiogenic properties. While the mechanism of action for interferon alpha in carcinoid tumor is not completely understood, a recent in vitro study showed that interferon alpha decreased transcription of VEGF gene expression through a Sp1 and/or Sp3 dependent inhibition of VEGF promoter activity. (18) Thus, there is rationale for potential synergy between these compounds in combination. Studies using the combination of interferon and bevacizumab are ongoing in melanoma, renal cell carcinoma, and carcinoid.

Interferon has been combined with somatostatin analogues in two random assignment studies. In one study, carcinoid patients who have undergone debulking by surgery and hepatic artery embolization were randomly assigned to octreotide or octreotide plus interferon. A significant improvement in time to progression was observed in the interferon arm (HR = 0.28, 95% CI (.16-.45). (19) In a second random assignment trial, patients were treated with lanreotide, interferon, or lanreotide plus interferon. Objective response rates were 4%, 4% and 7%. *(20)* Although there is no defined standard therapy for carcinoid, in patients with progressive disease, octreotide plus interferon is considered an accepted systemic therapy option by National Comprehensive Cancer Network and European Neuroendocrine Tumor Society and is therefore the control arm in this study. (21,22)

Bevacizumab in carcinoid tumors

Carcinoid tumors are vascular tumors with often accompanying desmoplastic reaction. Studies into the roles of various growth factors in carcinoid tumors and tumor stroma have been performed by various investigators. Vascular endothelial growth factor (VEGF) expression has been demonstrated in both gastrointestinal and pulmonary carcinoid. (23,24) Cecal transplantations using cells obtained from liver metastasis of human duodenal carcinoid have been performed in mice. In this model, compared to no treatment controls, treatment with VEGF monoclonal antibody resulted in significant tumor growth inhibition and reduction in number of liver metastases. *(25)*

In a recent Phase II trial with bevacizumab and peg-interferon alpha that has completed accrual, patients were randomly assigned to 18 weeks of treatment with either octreotide plus bevacizumab (BVZ) or octreotide plus peginterferon (PEGI). At earliest evidence of disease progression or conclusion of 18 weeks, patients were treated with all three drugs until disease progression. In this trial, decreased tumor perfusion was observed within 48 hours of treatment with BVZ by functional CT. *(26)* Sustained decrease in tumor perfusion at Week 18 (21 days after the previous dose of bevacizumab) was also observed. By RECIST criteria, 4 PR (4 BVZ, 0 PEGI), 33 SD (17 BVZ, 16 PEGI), and 7 PD (1 BVZ, 6 PEGI) have been observed. An additional patient achieved PR on BVZ + PEGI following PD on PEGI alone. Sixteen patients remain on

study. PFS duration was superior in the BVZ arm (P=.02). PFS rates after 18 weeks of monotherapy were 96% in BVZ versus 68% on the PEGI arm. During the 18 weeks of monotherapy, ≥ 50% reduction in 5HIAA was observed in 19% on BVZ and 31% on PEGI. Overall, 46% achieved ≥ 50% reduction in 5HIAA.

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. We are unaware of any literature supporting an interactive treatment effect by sex or race. Therefore, SWOG does not have current plans to alter the accrual for separate gender or racial subsets. The Group is committed to the continued accrual of non-white patients to all of its trials at current levels or better, and will explore the effect of treatment by race and sex in these trials. Anticipated accrual to this study by race and ethnicity, based on previous Group trials in this disease type, follows:

	Females	Males	Total
Hispanic	8	4	12
Not Hispanic	180	208	388
Total	188	212	400

American Indian	0	0	0
Asian	4	4	8
Black	16	16	32
Pacific Islander	0	0	0
White	168	192	360
Total	188	212	400

3.0 DRUG INFORMATION

3.1 Bevacizumab (rhuMAb VEGF) (Avastin®) (NSC #704865) (IND #113918)

a. DESCRIPTION

Bevacizumab is a recombinant humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) resulting in inhibition of angiogenesis. Of the identified angiogenic factors, vascular endothelial growth factor (VEGF; also known as vascular permeability factor) is the most potent and specific and has been identified as a crucial regulator of both normal and pathologic angiogenesis. VEGF produces a number of biologic effects, including endothelial cell mitogenesis and migration, induction of proteinases leading to remodeling of the extracellular matrix, increased vascular permeability, maintenance of survival for newly formed blood vessels, and, possibly, suppression of dendritic cell antigen presentation. The biologic effects of VEGF are mediated through binding and stimulation of two receptors on the surface of endothelial cells: Flt-1 (fms-like tyrosine kinase)/VEGFR-1 and KDR (kinase domain region)/VEGFR-2.

Increased levels of VEGF expression have been found in most human tumors examined to date, including tumors of the lung, breast, thyroid, gastrointestinal tract, kidney, bladder, ovary, and cervix, angiosarcomas, glioblastomas, as well as multiple myeloma, lymphoma, and AML. Inhibition of VEGF using an anti-VEGF monoclonal antibody blocks the growth of a number of human cancer cell lines in nude mice. The human cancers represented by these cell lines that

are growth-inhibited by anti-VEGF antibody include non–small cell lung cancer (Calu-6), colorectal cancer (LS174T, HM-7, LSLiM6), breast cancer (MCF-7), prostate cancer (D-145), head and neck cancer (KB), ovarian cancer (SK-OV-3), and others.

b. TOXICOLOGY

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Bevacizumab (rhuMAb VEGF, NSC 704865)

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 (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 3540 patients.* Below is the CAEPR for bevacizumab (rhuMAb VEGF)

Version 2.4, May 23, 2016[1]

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term) [n= 3540]			**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)***
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
CARDIAC DISORDERS			
		Acute coronary syndrome[2]	
	Cardiac disorders - Other (supraventricular arrhythmias)[3]		***Cardiac disorders - Other (supraventricular arrhythmias)[3] (Gr 3)***
		Heart failure	

CARDIAC DISORDERS (contd.)			
		Left ventricular systolic dysfunction	
		Myocardial infarction[2]	
		Ventricular arrhythmia	
		Ventricular fibrillation	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Colitis		***Colitis (Gr 3)***
	Constipation		***Constipation (Gr 3)***
	Diarrhea		***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[4]	
	Gastrointestinal hemorrhage[5]		***Gastrointestinal hemorrhage[5] (Gr 2)***
	Gastrointestinal obstruction[6]		
		Gastrointestinal perforation[7]	
		Gastrointestinal ulcer[8]	
	Ileus		
	Mucositis oral		***Mucositis oral (Gr 3)***
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 3)***
	Infusion related reaction		***Infusion related reaction (Gr 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 3)***
	Pain		***Pain (Gr 3)***
HEPATOBILIARY DISORDERS			
		Gallbladder perforation	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 2)***
		Anaphylaxis	

INFECTIONS AND INFESTATIONS			
	Infection[9]		***Infection[9] (Gr 3)***
		Infections and infestations - Other (necrotizing fasciitis)	
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Injury, poisoning and procedural complications - Other (anastomotic leak)[10]	
	Wound complication		***Wound complication (Gr 2)***
	Wound dehiscence		***Wound dehiscence (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 3)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hyperglycemia		
	Hypokalemia		
	Hyponatremia		

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 3)***
		Avascular necrosis[11]	
	Generalized muscle weakness		
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[12]		
	Myalgia		***Myalgia (Gr 3)***
	Osteonecrosis of jaw[13]		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
		Intracranial hemorrhage	
		Ischemia cerebrovascular[2]	
	Peripheral sensory neuropathy[14]		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Hematuria		***Hematuria (Gr 3)***
	Proteinuria		***Proteinuria (Gr 2)***
		Renal and urinary disorders - Other (nephrotic syndrome)	
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Reproductive system and breast disorders - Other (ovarian failure)[15]			
		Vaginal fistula	
	Vaginal hemorrhage		***Vaginal hemorrhage (Gr 3)***

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr 3)***
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		***Cough (Gr 3)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		***Epistaxis (Gr 3)***
	Hoarseness		***Hoarseness (Gr 3)***
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 3)***
		Vascular disorders - Other (arterial thromboembolic event)[2,16]	

[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] The risks of arterial thrombosis such as cardiac or CNS ischemia are increased in elderly patients and in patients with a history of diabetes.

[3] Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation, and atrial flutter.

[4] Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.
[5] Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.
[6] Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.
[7] Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation.
[8] Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.
[9] Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.
[10] Anastomotic leak may include Gastric anastomotic leak; Gastrointestinal anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak.
[11] There have been reports of non-mandibular osteonecrosis (avascular necrosis) in patients under the age of 18 treated with bevacizumab.
[12] Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.
[13] Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.
[14] Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.
[15] Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.
[16] Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

Adverse events reported on bevacizumab (rhuMAb VEGF) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that bevacizumab (rhuMAb VEGF) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Bone marrow hypocellular; Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrioventricular block complete; Atrioventricular block first degree; Cardiac arrest; Myocarditis; Pericardial effusion; Restrictive cardiomyopathy; Right ventricular dysfunction
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (tympanic membrane perforation); Hearing impaired; Tinnitus; Vertigo

ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blindness); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (corneal epithelial defect); Eye disorders - Other (floaters); Eye disorders - Other (ischemic CRVO); Eye disorders - Other (macular pucker); Eye disorders - Other (transient increased IOP > or =30 mm Hg); Eye disorders - Other (vitreous hemorrhage); Eye pain; Keratitis; Optic nerve disorder; Photophobia; Retinal detachment; Retinal tear; Retinopathy; Watering eyes
GASTROINTESTINAL DISORDERS - Ascites; Chelitis; Colonic stenosis; Dry mouth; Dysphagia; Enterocolitis; Esophageal pain; Esophageal stenosis; Flatulence; Gastrointestinal disorders - Other (peritonitis); Oral pain; Pancreatitis; Proctitis; Rectal mucositis; Rectal stenosis; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema face; Edema limbs; Edema trunk; Facial pain; Fever; Flu like symptoms; Gait disturbance; Injection site reaction; Localized edema; Multi-organ failure; Sudden death NOS
HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder necrosis; Gallbladder obstruction; Hepatic failure; Hepatic necrosis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Arterial injury; Bruising; Burn; Dermatitis radiation; Fracture
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood antidiuretic hormone abnormal; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Electrocardiogram QT corrected interval prolonged; Forced expiratory volume decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Chest wall pain; Fibrosis deep connective tissue; Head soft tissue necrosis; Joint effusion; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neck pain; Pain in extremity; Pelvic soft tissue necrosis; Soft tissue necrosis lower limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Arachnoiditis; Ataxia; Central nervous system necrosis; Cerebrospinal fluid leakage; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Facial nerve disorder; Hydrocephalus; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (increased intracranial pressure); Paresthesia; Peripheral motor neuropathy; Pyramidal tract syndrome; Seizure; Somnolence; Tremor; Vasovagal reaction
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Libido decreased; Psychosis
RENAL AND URINARY DISORDERS - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Renal and urinary disorders - Other (dysuria); Renal and urinary disorders - Other (ureterolithiasis); Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain; Erectile dysfunction; Irregular menstruation; Pelvic pain; Vaginal discharge
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Atelectasis; Hypoxia; Nasal congestion; Pulmonary fibrosis; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (dry nares); Respiratory, thoracic and mediastinal disorders - Other (pulmonary infarction)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Hyperhidrosis; Nail loss; Pain of skin; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders - Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Skin ulceration; Stevens-Johnson syndrome
VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Lymphocele; Phlebitis; Vasculitis

Note: Bevacizumab (rhuMAb VEGF) 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.

Based on clinical trials with bevacizumab as monotherapy or in combination with chemotherapy, the most common adverse events of any severity include asthenia, pain, headache, hypertension, diarrhea, stomatitis, constipation, epistaxis, dyspnea, dermatitis and proteinuria. The most common Grade 3-4 adverse events were asthenia, pain, hypertension, diarrhea and leukopenia. The most serious AEs include life-threatening or fatal hemorrhage, arterial thromboembolic events, gastrointestinal perforation and wound dehiscence; these events were uncommon but occurred at an increased frequency compared to placebo or chemotherapy controls in randomized studies.

The following is a description of major adverse events associated with bevacizumab therapy. Reference may also be made to the Investigator's Brochure for bevacizumab. The Package Insert (or Full Prescribing Information) was prepared for commercial Avastin but not the investigational bevacizumab being used in this protocol. The Package Insert should therefore only be used in combination with the Investigator's Brochure.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome: RPLS or clinical syndromes related to vasogenic edema of the white matter have been rarely reported in association with bevacizumab therapy (< 1%). Clinical presentations are variable and may include altered mental status, seizure and cortical visual deficit. HTN is an common risk factor and was present in most (though not all) patients on bevacizumab who developed RPLS. MRI scans are key to diagnosis and typically demonstrate vasogenic edema (hyperintensity in T2 and FLAIR images and hypointensity in T1 images) predominantly in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the gray matter may also be involved. RPLS should be in the differential diagnosis in patients presenting with unexplained mental status change, visual disturbance, seizure or other CNS findings. RPLS is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent progression to irreversible tissue damage.

Infusion-Related Reactions: Infusion reactions with bevacizumab were uncommon (< 3%) and rarely severe (0.2%). Infusion reactions may include rash, urticaria, fever, rigors, hypertension, hypotension, wheezing, or hypoxia. Currently, there is no adequate information on the safety of retreatment with bevacizumab in patients who have experienced severe infusion-related reactions.

Hypertension: Hypertension is common in patients treated with bevacizumab, with an incidence of 20-30% across trials. Initiation or increase of anti-hypertensive medications may be required, but in most cases, blood pressure (BP) can be controlled with routine oral drugs. However, incidents of hypertensive crisis with encephalopathy or cardiovascular sequelae have been rarely reported. BP should be closely monitored during bevacizumab therapy and the goal of BP control should be consistent with general medical practice. Bevacizumab therapy should be suspended in the event of uncontrolled hypertension.

Proteinuria: Proteinuria has been seen in all bevacizumab studies to date, ranging in severity from an asymptomatic increase in urine protein (incidence of about 20%) to rare instances of nephrotic syndrome (0.5% incidence). Pathologic findings on renal biopsies in two patients showed proliferative glomerulonephritis. NCI-CTCAE Grade 3 proteinuria (> 3.5 gm/24 hour urine) is uncommon, but the risk may be higher in patients with advanced RCC. In the Phase II randomized study in RCC, 24-hour urine was collected in a subset of patients enrolled, and Grade 3 proteinuria was found in 4 patients in the 10 mg/kg-arm (n=37), 2 patients in the 3mg/kg arm (n=35) and none in the placebo arm (n=38). The safety of continuing bevacizumab in patients with moderate or severe proteinuria has not been adequately tested.

Hemorrhage: The incidence of hemorrhage is increased with bevacizumab therapy. Epistaxis is common, occurring in 20-40% of patients, but it is generally mild and rarely requires medical intervention. Life-threatening and fatal hemorrhagic events have been observed in bevacizumab studies and included pulmonary hemorrhage, CNS bleeding and gastrointestinal (GI) bleeding. In a Phase II study in non-small cell lung cancer, 6 cases of life-threatening hemoptysis or hematemesis were reported among 66 patients treated with bevacizumab and chemotherapy; 4 of these events were fatal (Novotny et al., 2001). In the pivotal Phase III trial in advanced colorectal cancer, the rate of GI hemorrhage (all grades) was 24% in the IFL/bevacizumab arm compared to 6% in the IFL arm; Grade 3-4 hemorrhage was 3.1% for IFL/bevacizumab and 2.5% for IFL. Serious GI hemorrhage has also been observed in clinical trials with bevacizumab in patients with pancreatic cancer or varices treated with bevacizumab.

Arterial Thromboembolic Events: The risk of arterial thromboembolic events is increased with bevacizumab therapy, and such events included cerebral infarction, transient ischemic attack (TIA), myocardial infarction and other peripheral or visceral arterial thrombosis. In the pivotal trial in CRC (AVF2107), the incidence of arterial thromboembolic events was 1% in the IFL/placebo arm compared to 3% in the IFL/ bevacizumab arm. A pooled analysis of five randomized studies showed a two-fold increase in these events (4.4% vs. 1.9%). Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk (Schilling et al., ASCO 2005). In patients ≥ 65 years treated with bevacizumab and chemotherapy, the rate of arterial thromboembolic events was approximately 8.5%.

Gastrointestinal Perforation/Fistula: GI perforations/fistula were rare but occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal Phase III trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving 5-FU/bevacizumab compared to 0.3% in patients receiving IFL alone. GI perforation has also been reported in patients with gastric/esophageal cancer, pancreatic cancer, ovarian cancer or comorbid GI conditions such as diverticulitis and gastric ulcer. GI perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain or rectal/abdominal abscess.

Wound Healing Complications: Bevacizumab delays wound healing in rabbits, and it may also compromise or delay wound healing in patients. Bowel anastomotic dehiscence and skin wound dehiscence have been reported in clinical trials with bevacizumab. The appropriate interval between surgery and initiation of bevacizumab required to avoid the risk of impaired wound healing has not been determined. However, all clinical trials with bevacizumab have required a minimum of 28 days from prior major surgery; experience in the pivotal trial in advanced CRC suggests that initiation of bevacizumab 29-50 days following surgery should be associated with a very low incidence of wound dehiscence. The optimal interval between termination of bevacizumab and subsequent elective surgery has not been determined either. In the pivotal study in CRC, 40 patients on the IFL/bevacizumab arm and 25 patients on the ILF/placebo arm underwent major surgery while on study; among them, significant post-operative bleeding or wound healing complications occurred in 4 of the 40 patients from the IFL/bevacizumab arm and none of the 25 patients from the IFL alone arm. Decisions on the timing of elective surgery should take into consideration the half-life of bevacizumab (average 21 days, with a range of 11-50 days).

Congestive Heart Failure: The risk of left ventricular dysfunction may be increased in patients with prior or concurrent anthracycline treatment. In a Phase III controlled clinical trial in metastatic breast cancer (AVF 2119g) in which all patients had received prior anthracyclines, congestive heart failure (CHF) or cardiomyopathy were reported in 7 patients (3%) in the bevacizumab/capecitabine arm compared to 2 (1%) in the capecitabine-only arm. No increase in CHF was observed in CRC trials with bevacizumab in combination with IFL or 5-FU.

Venous Thrombosis: Venous thromboembolic events reported in bevacizumab trials included lower extremity deep vein thrombosis (DVT), pulmonary embolism and rarely, mesenteric or portal vein thrombosis. In the pivotal Phase III trial of IFL + bevacizumab (given at 5 mg/kg q2w), the overall incidences of Grade 3-4 venous thromboembolic events were comparable in the two arms (15.1 vs. 13.6%).

Fertility and Pregnancy: Clinical data are lacking regarding the immediate or long-term effect of bevacizumab on fertility and pregnancy. However, bevacizumab is known to be teratogenic and detrimental to fetal development in animal models. In addition, bevacizumab may alter corpus luteum development and endometrial proliferation, thereby having a negative effect on fertility. As an IgG1, it may also be secreted in human milk. Therefore, fertile men and women on bevacizumab studies must use adequate contraceptive measures and women should avoid breast feeding. The duration of such precautions after discontinuation of bevacizumab should take into consideration the half-life of the agent (average 21 days, with a range of 11 to 50 days).

Immunogenicity: As a therapeutic protein, there is a potential for immunogenicity with bevacizumab. With the currently available assay with limited sensitivity, high titer human anti-bevacizumab antibodies have not been detected in approximately 500 patients treated with bevacizumab.

c. PHARMACOLOGY

Kinetics: In study AVF0737g, the pharmacokinetics of bevacizumab appeared to be linear for doses of ≥ 1 mg/kg, with a half-life of ~15 days. A consistent profile was seen in study AVF0761g. Co-administration of bevacizumab with cytotoxic chemotherapy did not appear to result in a change in the systemic concentrations of the cytotoxic agents.

How Supplied: Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. For bevacizumab, each 400 mg (16 mL) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

Preparation: Vials contain no preservative and are intended for single use only. Place the calculated dose in 100 mL of 0.9% sodium chloride for Injection. Once the bevacizumab has been added to the bag with 0.9% Sodium Chloride for Injection, the solution must be administered within 8 hours. When the bevacizumab IV bag is empty, an additional 50 ml of 0.9% Sodium Chloride for Injection should be added to the IV bag and the infusion continued for a volume equal to that of the tubing to insure complete delivery of the bevacizumab. An alternative method of flushing the infusion line would be to replace the empty bevacizumab infusion bag with a 50 mL bag of 0.9% Sodium Chloride for Injection and infuse a volume equal to that of the tubing to insure complete delivery of the bevacizumab. Note that this flush is not included in the infusion times.

Storage and Stability: Bevacizumab is only shipped Monday through Thursday. It is shipped on blue ice for next day delivery. On receipt, bevacizumab should be stored in the refrigerator (2^{o} to 8^{o}C) and should remain refrigerated until just prior to use. Do not freeze. Do not shake. Shelf-life studies of bevacizumab are continuing. Investigators will be notified of any dating extensions, when lots have expired, and how to handle disposition of the agent. The sterile single use vials contain no antibacterial preservatives. Therefore, vials should be discarded 8 hours after initial entry. Once diluted in 0.9% Sodium Chloride for Injection, solution of bevacizumab must be administered within 8 hours.

Administration: The route of administration is intravenous as a continuous infusion. The initial dose should be administered over a minimum of 90 minutes. If no adverse reactions occur after the initial dose, the second dose should be administered over a minimum of 60 minutes. If no adverse reactions occur after the second dose, all subsequent doses should be administered 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.

d. SUPPLIER

Bevacizumab is investigational and will be supplied by the NCI for this study.

Drug 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 drug 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 and a CV. 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.

Drug may be requested by completing a Clinical Drug Request (NIH-986) and mailing it to the Drug Management and Authorization Section, PMB, DCTD, NCI, 9900 Rockville Pike, EPN Room 707, Bethesda, MD 20892-7422 or faxing it to 301/480-4612. For questions call 301/496-5725.

Drug Returns: All unused drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.info.nih.gov) or by calling the PMB at 301/496-5725.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (http://ctep.info.nih.gov) or by calling the PMB at 301/496-5725.

Questions about drug orders, transfers, returns or accountability should be addressed to the PMB by calling 301/496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern Time.

3.2 Interferon Alpha-2b (Intron-A) (NSC-377523)

a. DESCRIPTION

Interferon alpha-2b recombinant is a water soluble protein with a molecular weight of 19,271 daltons produced by recombinant DNA techniques.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Once bound, interferon initiates a complex sequence of intracellular events resulting in inhibition of viral replication, suppression of cell proliferation, augmentation of the phagocytic activity of macrophages, and augmentation of the specific cytotoxicity of lymphocytes for target cells.

b. TOXICOLOGY

Human Toxicity: The major toxicity of alpha interferon is a "flu-like" syndrome which occurs in a dose-dependent fashion and consists of fatigue, fever, chills, myalgias, and headache. These symptoms tend to diminish with continuing therapy. Other side effects include anemia, thrombocytopenia, leukopenia, anorexia, nausea, vomiting, diarrhea, dyspepsia, dysphagia, abdominal pain, dizziness, rash, dryness or inflammation of the oropharynx, dry skin or pruritis, weight loss, diaphoresis, paresthesias, partial alopecia, reactivation of herpes labialis, transient impotence, arthralgias, increases in bilirubin, LFTs and alkaline phosphatase. Renal/bladder toxicities include microscopic hematuria, pyuria, azotemia, proteinuria, acute renal failure, glycosuria and albuminuria. Rarely, CNS effects are seen to include numbness, confusion, paresthesia, inability to concentrate, depression, dry mouth, encephalopathy, seizure, coma, psychomotor retardation, syncope, hemianopsia, taste change, aphasia, neuropathy, tremors, somnolence, hallucinations, memory dysfunction, personality disorder, anxiety, eye pain, and agitation. Rare adverse cardiac events have included hypertension, hypotension, chest pain, arrhythmias, palpitations and myocardial infarction. Pulmonary toxicities include orthopnea, dyspnea, coughing, and pulmonary edema/ARDS. Some patients have experienced hyperglycemia, increased clotting times and cyanosis.

c. PHARMACOLOGY

Kinetics: Elimination half-life after SQ or IM administration was approximately 2 - 3 hours, with levels below detection limits by 16 hours. With IV administration, serum concentrations peaked by the end of infusion and were undetectable 4 hours after infusion. Serum-neutralizing antibodies have been detected but are low in occurrence. The clinical significance of this is unknown.

Formulation: Powder for Injection - The 3, 5, 18, 25 and 50 million IU packages are to be used for intramuscular or subcutaneous injection and are supplied with an accompanying diluent. The 10 million IU package is for intramuscular, subcutaneous or intralesional injection. Solution for Injection - The 10 and 25 million IU packages are for use by intramuscular or subcutaneous injection, and not for intralesional use. The alpha interferon should be reconstituted with Sterile Water for Injection, USP. Data on file at Schering indicates that the admixture of alpha interferon in 0.9% Sodium Chloride is stable up to 24 hours when all of the following conditions are met:

1. Storage is between 2 and 25°C (36 and 77°F).

2. Concentration of alpha interferon is 1 x 10^5 IU/ml or greater.

3. Parenteral container is made of glass or the following plastic parenteral containers: Lifecare® minibag from Abbott or Viaflex® minibag from Travenol (USA version only).

Since interferons adhere to glass and plastic, special care must be taken when working with low concentrations since the potential exists to lose a greater percentage of activity.

Alpha interferon is not compatible with the Travenol Infusor. It is incompatible with 5% Dextrose Injection, USP.

Storage: Lyophilized powder, accompanying diluent, reconstituted solution and injectable solution - Vials must be stored in a secured refrigerator at 2 - 8°C (36 - 46°F). DO NOT FREEZE OR SHAKE.

Administration: Interferon alpha-2b is administered by subcutaneous injection.

Please refer to the complete prescribing information for additional details.

d. SUPPLIER

Interferon alpha-2b is commercially available and should be purchased through a third party. This drug will not be supplied by the NCI.

3.3 Octreotide acetate for injectable suspension (Sandostatin LAR® Depot) (Octreotide LAR Depot)

a. DESCRIPTION

Octreotide is the acetate salt of a cyclic octapeptide. It is a long-acting octapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin. Octreotide is known chemically as L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxy-methyl) propyl]-, cyclic (2→7)-disulfide; [R-(R*,R*)].

Sandostatin LAR® depot (octreotide acetate for injectable suspension) is available in a vial containing the sterile drug product, which when mixed with diluent, becomes a suspension that is given as a monthly intragluteal injection. The octreotide is uniformly distributed within the microspheres which are made of a biodegradeable glucose star polymer, D,L-lactic and glycolic acids copolymer. Sterile mannitol is added to the microspheres to improve suspendability. Octreotide LAR depot is available as sterile 5 mL vials in 3 strengths delivering 10 mg, 20 mg or 30 mg octreotide free peptide.

Octreotide exerts pharmacologic actions similar to the natural hormone, somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin, it also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

By virtue of these pharmacological actions, octreotide has been used to treat the symptoms associated with metastatic carcinoid tumors (flushing and diarrhea), and Vasoactive Intestinal Peptide (VIP) secreting adenomas (watery diarrhea). Octreotide substantially reduces and in many cases can normalize growth hormone and/or IGF-1 (somatomedin C) levels in patients with acromegaly. Single doses of Sandostatin® Injection given subcutaneously have been shown to inhibit gallbladder contractility and to decrease bile secretion in normal volunteers. In controlled clinical trials the incidence of gallstone or biliary sludge formation was markedly increased. Octreotide may cause clinically significant suppression of thyroid stimulating hormone (TSH).

b. TOXICOLOGY

Octreotide is generally well-tolerated in patients with carcinoid tumors. Toxicities may include:

Gastrointestinal: Diarrhea (34-60%), abdominal pain (10%) or discomfort, flatulence, constipation, nausea, vomiting (10%), biliary sludge, gallstone (22-33%), bowel obstruction (rare), pancreatitis (rare), steatorrhea (6%).

Endocrine: hypoglycemia (3%), hyperglycemia (27%), galactorrhea, gynecomastia, flushing, hypothyroidism (12%).

Cardiac: bradycardia (25%), abnormal ECG, cardiac dysrhythmia (10%), hypertension (rare).

Dermatologic effects: alopecia (>10%), injection site pain (20-50%), rash (rare)

Hepatic effects: hepatitis (rare)

Musculoskeletal effects: Rarely, back pain, myalgia, arthralgia, muscle cramps, shoulder pain and leg pain have been reported.

Neurologic effects: Rarely, fatigue, headache, insomnia, vertigo, and dizziness have been reported.

Psychiatric effects: Anxiety, confusion, and depression have rarely occurred with octreotide use.

Hematology findings: Rarely, thrombocytopenia has been reported.

c. PHARMACOLOGY

Kinetics: After a single IM injection of the long-acting depot dosage form octreotide LAR depot in healthy volunteer subjects, the serum octreotide concentration reached a transient initial peak of about 0.03 ng/mL/mg within 1 hour after administration progressively declining over the following 3 to 5 days to a nadir of < 0.01 ng/mL/mg, then slowly increasing and reaching a plateau about two to three weeks post injection. Plateau concentrations were maintained over a period of nearly 2-3 weeks, showing dose proportional peak concentrations of about 0.07 ng/mL/mg. After about 6 weeks post injection, octreotide concentration slowly decreased, to < 0.01 ng/mL/mg by weeks 12 to 13, concomitant with the terminal degradation phase of the polymer matrix of the dosage form. The relative bioavailability of the long-acting release octreotide LAR depot compared to immediate-release Sandostatin® Injection solution given subcutaneously was 60 - 63%.

In patients with acromegaly, the octreotide concentrations after single doses of 10 mg, 20 mg, and 30 mg octreotide LAR depot were dose proportional. The transient day 1 peak, amounting to 0.3 ng/mL, 0.8 ng/mL, and 1.3 ng/mL, respectively, was followed by plateau concentrations of 0.5 ng/mL, 1.3 ng/mL, and 2.0 ng/mL, respectively, achieved about 3 weeks post injection. These plateau concentrations were maintained for nearly two weeks.

Following multiple doses of octreotide LAR depot given every 4 weeks, steady-state octreotide serum concentrations were achieved after the third injection. Concentrations were dose proportional and higher by a factor of approximately 1.6 to 2.0 compared to the concentrations after a single dose. The steady-state octreotide concentrations were 1.2 ng/mL and 2.1 ng/mL, respectively, at trough and 1.6 ng/mL and 2.6 ng/mL, respectively, at peak with 20 mg and 30 mg octreotide LAR depot given every 4 weeks. No accumulation of octreotide beyond that expected from the overlapping release profiles occurred over a duration of up to 28 monthly injections of octreotide LAR depot. With the long-acting depot formulation octreotide LAR depot administered IM every 4 weeks the peak-to-trough variation in octreotide concentrations ranged from 44 to 68%, compared to the 163 to 209% variation encountered with the daily subcutaneous t.i.d. regimen of Sandostatin® Injection solution.

In patients with carcinoid tumors, the mean octreotide concentrations after 6 doses of 10 mg, 20 mg, and 30 mg octreotide LAR depot administered by IM injection every four weeks were 1.2 ng/mL, 2.5 ng/mL, and 4.2 ng/mL, respectively. Concentrations were dose proportional and steady-state concentrations were reached after two injections of 20 and 30 mg and after three injections of 10 mg.

Octreotide LAR depot has not been studied in patients with renal impairment. Octreotide LAR depot has not been studied in patients with hepatic impairment.

Formulation: Sandostatin LAR® depot (octreotide acetate for injectable suspension) is available in single use kits containing a 5 mL vial of 10 mg, 20 mg or 30 mg strength, a 2 mL vial of diluent, a 5 mL sterile plastic syringe, two sterile 1½" 19 gauge needles, and three alcohol wipes. An instruction booklet for the preparation of drug suspension for injection is also included with each kit. Please see current Prescribing Information packaged with the Sandostatin LAR kit for additional information.

Storage: For prolonged storage, octreotide LAR depot should be stored at refrigerated temperatures 2°C - 8°C (36°F - 46°F) and protected from light until the time of use. Octreotide LAR depot drug product kit should remain at room temperature for 30-60 minutes prior to preparation of the drug suspension. However, after preparation the drug suspension must be administered.

Administration: Octreotide LAR depot is administered as an intramuscular (intragluteal) injection according to the package insert. An instruction booklet for the preparation of drug suspension for injection is also included with each kit.

Please refer to the complete prescribing information for additional details.

d. SUPPLIER

Octreotide LAR depot is commercially available and should be purchased through a third party. This drug will not be supplied by the NCI.

4.0 STAGING CRITERIA

Staging criteria are not applicable to this study.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the **S0518** Prestudy Form and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. If Day 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.1 REGISTRATION STEP 1

_____ a Patient must have unresectable metastatic or locally advanced, low- or intermediate-grade neuroendocrine carcinoma.

NOTE: Pathology report must state one of the following: Carcinoid, low-grade or well-differentiated neuroendocrine carcinoma, atypical carcinoid, intermediate-grade or moderately differentiated neuroendocrine carcinoma. Patients with poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, or goblet cell carcinoid are not eligible. Patient must not have osseous metastasis as only site of disease. Patients with medullary thyroid carcinoma or islet cell carcinoma are not eligible. If pathology report states only neuroendocrine carcinoma, pathology subtype must be reconfirmed.

Occasionally, it is not possible to establish tumor grade on FNA cytology material. If a new biopsy is needed, a core needle biopsy should be obtained whenever possible.

_____ b. Patient must have high risk disease as defined by at least one of the following:

1. Progressive disease

2. Refractory carcinoid syndrome while receiving octreotide (defined by > 2 flushing episodes/day or > 4 bowel movements/day)

3. Atypical histology and more than 6 lesions

4. Metastatic colorectal carcinoid. Patients with metastatic cecal or appendiceal carcinoid tumor are not eligible unless the tumors fit into one of the other high-risk categories (a, b, or c above).

5. Metastatic gastric carcinoid

SWOG Patient No.

Patient's Initials (L, F, M)

____ c. Patient must have measurable disease (see Section 10.0). CT or MRI used for tumor measurement must have been completed within 28 days prior to registration. X-rays, scans or other tests for assessment of non-measurable disease must have been performed within 42 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form. These scans also must be submitted for central radiology review (see Sections 5.1c, 15.1 and Appendix 18.5).

____ d. Institutions are required to submit CT/MRI scans as described in Section 15.1a and archived tissue for pathology review as described in Section 15.2a. Furthermore, institutions are required to seek additional patient consent for submission of octreotide scans as described in Section 15.1b, and submission of blood and use of archived tissue for correlative studies as described in Section 15.2b.

If patient consents to the submission of octreotide scans, the patient must also be registered to Registration Step 2 (see Sections 5.2a-5.2b).

____ e. Patient may have had up to one prior regimen of cytotoxic chemotherapy. At least 28 days must have elapsed since completion of prior therapy, and patient must have recovered from all effects.

____ f. Patient may have had prior hepatic artery embolization. At least 28 days must have elapsed since embolization and there must be residual measurable disease. Chemoembolization will be considered as one prior chemotherapy regimen.

____ g. Patient must not have received prior interferon, bevacizumab or any other therapy targeting VEGF or VEGF receptors (i.e., SU11248, PTK/ZK, BAY 43-9006, GW786034).

____ h. Patient may have received prior therapy targeting c-kit, abl, PDGFR, mTOR, and somatostatin receptors (not counted toward prior cytotoxic chemotherapy).

____ i. Prior radiation is allowed. There must be measurable disease. If prior therapies include peptide receptor radiotherapy, the target lesion(s) must have shown disease progression. At least 28 days must have elapsed since completion of prior therapy, and patient must have recovered from all effects.

____ j. Patients must have recovered from any prior surgery. One week must have elapsed from the time of a minor surgery and 4 weeks from major surgery.

____ k. At least 21 days must have elapsed since any prior octreotide LAR depot treatment.

____ l. Patient must have a Zubrod performance status of 0-2 (see Section 10.4).

____ m. Patient must have ANC > 1,500/mcl, hemoglobin > 8 g/dl, and platelets > 100,000/mcl within 28 days prior to registration.

____ n. Patient must have adequate liver function as evidenced by serum bilirubin < 1.5 x institutional upper limit of normal (IULN) and either SGOT or SGPT ≤ 2.5 x IULN obtained within 28 days prior to registration.

SWOG Patient No. _____

Patient's Initials (L, F, M)

_____ o. Patient must have adequate renal function as evidenced by serum creatinine < 1.5 mg/dL obtained within 28 days prior to registration.

_____ p. Urine protein must be screened by urine analysis for Urine Protein Creatinine (UPC) ratio. For UPC ratio > 0.5, 24-hour urine protein must be obtained and the level must be < 1,000 mg for patient enrollment. These results must be obtained within 28 days prior to registration.

Note: UPC ratio of spot urine is an estimation of the 24-hour urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm. UPC ratio is calculated using one of the following formulas:

[urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL [(urine protein) x 0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

_____ q. Patients not on anticoagulation must have PT and PTT ≤ 1.1 x lULN obtained within 28 days prior to registration. Patients on full-dose anticoagulation (warfarin or low molecular weight heparin) are eligible provided that both of the following criteria are met:

The patient has an in-range INR (usually between 2 and 3) on a stable dose of oral anticoagulant or on a stable dose of low molecular weight heparin.

The patient has no active bleeding or pathological condition that carries a high risk of bleeding such as varices.

_____ r. Patient must not have history or evidence of clinically significant peripheral vascular disease such as non-healing peripheral ulcers or claudication.

_____ s. Patient must not have a history of primary brain tumor or metastatic cancer to the brain. Brain imaging studies are not required for eligibility if the patient has no neurological signs or symptoms. If brain imaging studies are performed, they must be negative for disease.

_____ t. Patient must not have a history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to registration.

_____ u. Patient must not have history within the past 5 years or presence of bleeding diathesis or coagulopathy that results in spontaneous bleeding (in the absence of trauma) requiring pRBC transfusion.

_____ v. Patient must not have a serious (requiring active medical therapy with medication or medical device under the supervision of a physician) non-healing wound, ulcer, or bone fracture.

_____ w. Patient must not have recent history (within 6 months prior to registration) of these arterial thromboembolic events: transient ischemic attack, cerebrovascular accident, unstable angina, myocardial infarction, or New York Heart Association Grade II or higher congestive heart failure (see Appendix 18.1).

_____ x. Patients with a history of hypertension must be well-controlled (blood pressure < 150/90), on a stable regimen of antihypertensive therapy.

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

_____ y. Patient must not have hemoglobinopathies (e.g., Thalassemia) or any other cause of hemolytic anemia.

_____ z. Patient must not plan to use any other concurrent chemotherapy, immunotherapy, hepatic artery embolization, hepatic artery chemoembolization, radiofrequency ablation, other tumor ablative procedure or radiotherapy while on protocol treatment.

_____ aa. Patient must not be pregnant or nursing because bevacizumab may be harmful to the developing fetus and newborn (see Section 3.0 for more detail). Male and female patients of reproductive potential must agree to employ an effective barrier method of birth control throughout protocol treatment and for up to 6 months following discontinuation of bevacizumab.

_____ bb. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, or other adequately treated in situ cancer, or any other cancer from which the patient has been disease free for five years.

_____ cc. All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

_____ dd. At the time of patient registration, the treating institution's name and ID number must be provided to the Data Operations Center in Seattle in order to ensure that the current (within 365 days) date of institutional re view board approval for this study has been entered into the data base.

5.2 REGISTRATION STEP 2 – SPECT SUBSTUDY

Patients who consent to the submission of octreotide scans (see Section 5.1d) must be registered to Registration Step 2. This registration may take place concurrently with Registration Step 1, or may take place after Registration Step 1, provided the octreotide scans are performed at the times indicated in Section 15.1.

_____ a. Patient must have registered to the main study (see Registration Step 1, Sections 5.1-5.1dd).

_____ b. Patient must have consented to the submission of octreotide scans as described in Section 15.1.

_____ c. An octreotide scan obtained within 28 days prior to Registration Step 1 must be available for submission.

6.0 STRATIFICATION FACTORS

Patients will be randomized to either Arm 1 (octreotide plus bevacizumab) or Arm 2 (octreotide plus interferon) using a dynamic balancing algorithm *(34)* with stratification based on*:*

a. Site: small bowel, cecum, appendix versus other sites

b. Disease progression after initial diagnosis: yes versus no. NOTE: Progression may occur either during prior treatment, after prior treatment, or after initial diagnosis in the absence of prior treatment. Progression is defined as objective tumor progression (see Section 10.0) measured by radiographic means. Institutions must submit a copy of a radiology report dated within 6 months of registration to document pre-registration progression (see Section 14.4a).

c. Histologic grade: low versus intermediate (atypical) grade

d. Prior octreotide: within 2 months of registration versus none within 2 months of registration

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Yao at 713/792-2828 or Dr. Strosberg at 813/745-7257. For dosing principles or questions, please consult SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Good Medical Practice

The following pre-study tests should be obtained within 28 days prior to registration in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviations would be acceptable if they do not affect patient safety in the clinical judgment of the treating physician. The Study Coordinator must be contacted if there are significant deviations in the values of these tests.

a. Albumin, calcium, glucose, alkaline phosphatase, LDH, electrolytes (Na, K, Cl, CO_2, Mg)

b. Patient should not have any immunologically mediated disease (e.g., inflammatory bowel disease [Chron's disease, ulcerative colitis], rheumatoid arthritis, idiopathic thrombocytopenia purpura, systemic lupus erythematosus, autoimmune hemolytic anemia, scleroderma, severe psoriasis).

c. Patient should not have any serious intercurrent infections, or nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the complications of this treatment.

d. Patient should not have psychiatric disorders rendering them incapable of complying with the requirements of the protocol.

7.2 Treatment

Patients will be randomized to Arm 1 or Arm 2.

a. Octreotide dosing

For patients who have received octreotide prior to study entry, the first on-study dose of depot octreotide should be administered ≥ 21 days after the last pre-study dose.

For patients who are octreotide naïve, a test dose of short-acting octreotide 100 mcg sq will be given. (Short-acting octreotide is typically given as a subcutaneous injection of 100-300 mcg two to four times per day as needed for diarrhea and flushing.) If patient tolerates the short-acting injection, the first dose of depot octreotide LAR may be given 1 hour later.

If patient does not tolerate the short-acting injection, they must be removed from protocol treatment. Patient will be considered intolerant of octreotide if they develop Grade 2 bradycardia, Grade 2 hypoglycemia (unless due to fasting or the use of hypoglycemics), and/or any other Grade 3-4 toxicities.

b. Arm 1: Octreotide LAR depot plus bevacizumab

AGENT	**DOSE**	**ROUTE**	**SCHEDULE***
Octreotide LAR depot	20 mg	IM	Day 1 of each cycle
Bevacizumab	15 mg/kg	IV infusion over 90 ± 15 minutes**	Day 1 of each cycle, immediately after octreotide LAR depot

* One cycle = 21 days
** If no adverse reactions occur, the second dose of bevacizumab should be given over a minimum of 60 minutes. If no adverse event occurs, third and subsequent doses should be administered over a minimum of 30 minutes. Infusions should be run in a volumetric infusion device. Infusions should be run over the shortest period that is well-tolerated.

c. Arm 2: Octreotide LAR depot plus interferon alpha 2-b

AGENT	**DOSE**	**ROUTE**	**SCHEDULE***
Octreotide LAR depot	20 mg	IM	Day 1 of each cycle
Interferon alpha-2b	5 million units	SC**	Three times per week (Days 1, 3, 5, 8, 10, 12, 15, 17, 19 of each cycle)***

* One cycle = 21 days
** Patients who are deemed competent to self-administer interferon may do so (see Appendix 18.4).
*** At the discretion of the treating investigator, patient may have a one-week break from interferon every six weeks. If such break is given, patient will not take interferon on Days 1, 3 and 5 of Cycles 3, 5, 7, etc.

d. Refer to Section 15.1b and Appendix 18.6 for details regarding an optional SPECT (octreotide scan) study.

7.3 Treatment and Follow-Up

Patients should be treated until progression (or until one of the other criteria listed in Section 7.5 is met). If the progression is based on CT/MRI assessments, this should be documented on the Follow-up Tumor Assessment Form. For assessments based on other tests (e.g., X-ray), please submit the reports documenting the progression. If patients are removed due to symptomatic deterioration, details should be documented in the comments section of the Off Treatment Notice and/or the Follow-Up Tumor Assessment Form.

If the follow-up scans are not definitive for progression, every effort should be made to continue treatment until clear documentation of progression.

For patients who are removed from protocol treatment prior to progression, follow-up assessments should be made until documentation of progression.

NOTE: Total abdominal and pelvic imaging should be performed at baseline and follow-up for all patients enrolled in the study. If the patient has or is suspected to have involvement of disease in the chest/lung at baseline, all subsequent radiographic evaluations will also include chest CT or MRI scans. Otherwise, chest scanning need only be performed if clinically indicated.

7.4 Concurrent therapy

No investigational or commercial agents or therapies other than those described below may be administered while on protocol treatment with the intent to treat the patient's malignancy.

The use of interferon for control of carcinoid syndrome in the bevacizumab arm is not allowed. Other medications used for the supportive therapy of carcinoid syndrome are allowed. Specifically, short acting octreotide may be used for control of carcinoid syndrome.

Other medications for diarrhea may be used on an as-needed basis. Steatorrhea due to somatostatin analogue may be managed by the usage of pancrealipase. Diarrhea due to short gut syndrome should be managed with cholestyramine.

7.5 Criteria for Removal from Protocol Treatment

a. Progression of disease (based on investigator assessment) or symptomatic deterioration (as defined in Section 10.2).

b. Unacceptable toxicity.

c. Treatment delay of interferon alpha-2b or bevacizumab > 4 weeks for any reason except proteinuria as outlined in Section 8.5. (Patients may have a longer delay or discontinuation of octreotide and remain on protocol treatment, providing the interferon alpha-2b or bevacizumab therapy is continued.)

d. The patient may withdraw from the study at any time for any reason.

7.6 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.7 Follow-Up Period

All patients will be followed until death or 3 years after registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 will be utilized for SAE reporting only. The CTCAE Version 4.0 is identified and located at the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 3.0 for routine toxicity reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.

8.2 General Considerations

a. If a patient requires greater than a 4 week delay of interferon alpha-2b or bevacizumab for recovery (except for proteinuria as outlined in Section 8.5), they must be removed from protocol treatment.

b. There are no dose escalations for bevacizumab or interferon. If a dose reduction is mandated by toxicity, there will be no dose re-escalation even if toxicity resolves.

c. If multiple toxicities are experienced, dose modification will be based on the toxicity requiring the largest dose reduction.

d. If patient permanently discontinues bevacizumab or interferon due to adverse events, patient will be considered off protocol treatment. Patient may stay on protocol treatment if octreotide is discontinued, providing the interferon alpha-2b or bevacizumab therapy is continued.

8.3 Octreotide LAR depot

Any decision to alter or discontinue depot octreotide dosing should be based on the treating investigator's clinical assessment of benefit versus toxicity. Reduction of the dose of depot octreotide should be considered for Grade 2, 3, or 4 bradycardia or for other Grade 3 or 4 toxicity attributed to depot octreotide (e.g., glycemic control, liver dysfunction) or new/increased gallstone formation. The next scheduled dose of depot octreotide may be held until recovery to ≤ Grade 1 toxicity. Subsequent depot octreotide doses may be reduced by 10 mg at the next injection. Patients may continue interferon or bevacizumab during this period unless toxicity is suspected by the investigator to be related to interferon or bevacizumab.

Any increase in dose of depot octreotide during the study should be done only if the investigator determines the need based on an increase in symptoms related to tumor secretory products. Escalation of octreotide use should be considered for patients with a daily mean of ≥ 4 bowel movements over a 2-week period and total of ≥ 5 flushing episodes during this period. In the event that such treatment is necessary, short acting octreotide acetate at a dose of 100-300 mcg BID or TID is recommended in place of

increasing the dose of depot octreotide therapy. Please administer short acting octreotide according to the approved product package insert and report dose administered and frequency appropriately. Depot octreotide dose should not be increased during this study unless the investigator considers it essential for treatment of an exacerbation of a carcinoid secretory syndrome. If increased, the dose of depot octreotide should not exceed 30 mg every 21 days.

8.4 Interferon alpha-2b

a. Dose levels

DOSE LEVEL	DOSE
0	5 million units
-1	3 million units
-2	2 million units
-3	1 million units

If a patient requires dose reduction beyond dose level -3, interferon alpha will be permanently discontinued and the patient will be considered off protocol treatment.

At the discretion of the treating investigator, patient may have a 1-week treatment break from interferon alpha every 6 weeks.

b. Hematologic toxicities

TOXICITY			DOSE MODIFICATIONS
ANC		Platelets	
≥ 750/mcl	and	≥ 80,000/mcl	Maintain current dose
500-749/mcl	and/or	50,000-79,999/mcl	Reduce 1 dose level
< 500/mcl	and/or	< 50,000/mcl	Hold interferon alpha until recovery to ANC > 1,500/mcl and platelets > 100,000/mcl. Then reduce 1 dose level.

c. Non-hematologic toxicities with possible, probable or definite attribution to interferon alpha

For clinically significant Grade 3-4 adverse events, hold interferon until recovered to ≤ Grade 1. For Grade 3 non-hematologic toxicities, reduce 1 dose level. For Grade 4 non-hematologic toxicities, reduce 2 dose levels.

8.5 Bevacizumab

EVENT	ACTION TO BE TAKEN
Hypertension	
The dose of bevacizumab should be held for resting SBP > 150 or resting DBP > 100 at the time of infusion. Dose should also be held for symptomatic hypertension regardless of grade or blood pressure level. Dose may be held for up to 4 weeks.	
No dose modifications for Grade 1-2 events.	
Grade 3	Medications should be used for blood pressure control. Ideal goal for blood pressure is < 140/80. If a new anti-hypertensive is to be added, the choice of drug is at the discretion of treating physician. Prior experience with bevacizumab-associated hypertension among carcinoid patients suggested dihydrophyridine calcium channel blockers and alpha adrenergic vasodilators were effective. In general, the dose of agents should be maximized prior to changing or adding new agents. Record any new anti-hypertensive added and whether blood pressure was adequately controlled. <u>Recommended anti-hypertensives</u>: • nifidipine (Procardia XL®, Adalat CC®) 30 to 90 mg q day • nicardipine (Cardine SR®) 30 to 60 mg BID • terazosin (Hytrin®) 2 to 10 mg per day • doxazosin (Cardura®) 1 to 2 mg q day If HTN cannot be controlled with medications, remove patient from protocol treatment.
Grade 4	Remove patient from protocol treatment.

Hemorrhage	
No dose modifications for Grade 1-2 events	
Grade 3	Patients who are also receiving full-dose anticoagulation will be removed from protocol treatment. All other patients will have study treatment held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Patients who experience a repeat Grade 3 hemorrhagic event will be removed from protocol treatment.
Grade 4	Remove patient from protocol treatment.
Allergic reactions or acute infusional reactions/cytokine release syndrome	
Grade 1-3	If infusion-related or allergic reactions occur, premeds should be given with the next dose, and infusion time may not be reduced for the subsequent infusion. Follow the guidelines in Section 7.2b for bevacizumab administration. **For patients with Grade 3 reactions, bevacizumab infusion should be stopped and not restarted on the same day. At the physician's discretion, patient may be removed from protocol treatment or treatment (including bevacizumab) may be re-instituted with premeds and at a rate of 90+15 min. If bevacizumab is re-instituted, the patient should be closely monitored for a duration comparable to or longer than the duration of the previous reactions.**
Grade 4	Remove patient from protocol treatment.

<table>
<tr><td colspan="3">Venous Thrombosis

No dose modifications for Grade 1-2 events

Grade 3/ Asymptomatic Grade 4: Hold bevacizumab. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be held 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 patient must be on a stable dose of low-molecular weight heparin. Or, if on warfarin, the patient must have an in-range INR (usually between 2 and 3) prior to restarting bevacizumab.
• The patient must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.
• The patient must not have had evidence of tumor involving major blood vessels on any prior CT scan.

Symptomatic Grade 4: Remove patient from protocol treatment.</td></tr>
<tr><td colspan="3">Arterial Thromboembolic event
(Angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)

Any grade: Remove patient from protocol treatment.</td></tr>
<tr><td rowspan="4">Proteinuria</td><td colspan="2">[Proteinuria should be monitored by urine analysis for urine protein creatinine (UPC) ratio prior to every other dose of bevacizumab]</td></tr>
<tr><td>UPC ratio
< 3.5</td><td>Continue bevacizumab.</td></tr>
<tr><td>UPC ratio
≥ 3.5</td><td>Hold bevacizumab until UPC recovers to < 3.5. If therapy is held for > 2 months due to proteinuria, remove patient from protocol treatment.</td></tr>
<tr><td>Grade 4 (nephrotic syndrome)</td><td>Remove patient from protocol treatment.</td></tr>
<tr><td>GI Perforation requiring medical or surgical therapy</td><td colspan="2">Remove patient from protocol treatment.</td></tr>
<tr><td>Wound dehiscence requiring medical or surgical therapy</td><td colspan="2">Remove patient from protocol treatment.</td></tr>
<tr><td>Platelets
< 50,000/mcl</td><td colspan="2">Hold bevacizumab until recovery to > 100,000/mcl</td></tr>
</table>

RPLS (Reversible Posterior Leukoencephalopathy Syndrome)	Bevacizumab should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure. Patient should be removed from protocol treatment. However, resumption of protocol treatment (including bevacizumab) may be considered in patients who have documented benefit from bevacizumab, provided that RPLS was mild and has completely resolved clinically and radiographically within 2-4 weeks. The decision to resume bevacizumab in these patients **MUST** be discussed with and approved by the Study Coordinator, Dr. Yao (in consultation with CTEP).	
Other clinically significant AEs attributable to bevacizumab (except controlled nausea/vomiting)	Grade 3	• Hold bevacizumab until symptoms resolve to ≤ Grade 1 • If treatment delay is > 4 weeks due to toxicity, remove patient from protocol treatment.
	Grade 4	• Remove patient from protocol treatment. • **Upon consultation with the study chair,** resumption of treatment (including bevacizumab) may be considered if a patient is benefiting from therapy, and the Grade 4 toxicity is transient, has recovered to < Grade 1 and is unlikely to recur with retreatment.

8.6 G-CSF

G-CSF is not permitted while on protocol treatment.

8.7 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Yao at 713/792-2828 or Dr. Strosberg at 813/745-7257.

8.8 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 Arm 1 - Octreotide LAR depot + Bevacizumab

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Ω	√
REQUIRED STUDIES	PRE	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	F/U Prior	F/UAfter
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	To Prog	Prog
PHYSICAL ∑															
History and Physical Exam	X				X			X			X			X	X
Weight and Performance Status	X				X			X			X			X	
Blood Pressure D	X				X			X			X				
Disease Assessment %	X										X			X	
Toxicity Notation		X			X			X			X			X#	X#
Baseline Abnormalities Assessment	X														
LABORATORY ∑															
CBC/Differential/Platelets/Hemoglobin	X				X			X			X				
Serum Creatinine	X				X			X			X				
UPC (urine protein creatinine) ratio §	X							X							
Bilirubin	X				X			X			X				
SGOT or SGPT	X				X			X			X				
PT and PTT	X				X			X			X				
Albumin, calcium, glucose, alkaline phosphatase, LDH, electrolytes (Na, K, Cl, CO2, Mg) ß	X														
Serum chromogranin A, neuronspecific enolase, urinary 5HIAA ¶	X										X				

Study Calendar 9.1 continued on next page. Click here for footnotes.

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Ω	√
REQUIRED STUDIES	PRE	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	F/U Prior	F/UAfter
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	To Prog	Prog
SPECIMEN SUBMISSION															
Archived tissue per Section 15.2a (Required)	X														
Blood per Section 15.2b (Recommended)	X				X										
IMAGING PROCEDURES ∑															
CT (or MRI) for disease assessment %	X										X			X	
SPECT (octreotide scan) per Section 15.1b (Recommended)	X									Xp					
TREATMENT ∑															
Octreotide LAR depot		X			X			X			X				
Bevacizumab		X			X			X			X				

Note: Forms are found in Section 18.0. Forms submission guidelines are found in Section 14.0.

Footnotes

∑ Protocol treatment and parameters will continue at these intervals until progression of disease or until patient has met any of the guidelines in Section 7.5.

∆ Blood pressure will be taken prior to each dose of bevacizumab.

% CT (or MRI) must be submitted for central radiology review (see Section 15.1 and Appendix 18.5). CT (or MRI) should be performed at baseline and every 9 weeks until progression using the same modality as the pre-study exam.

§ UPC will be repeated before every other treatment with bevacizumab.

ß These tests are recommended for pre-study (see Section 7.1).

¶ These tests are required for pre-study and should be performed at the time of each disease assessment if elevated at baseline.

Ω After off treatment prior to disease progression, x-rays/scans for disease assessment and physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 9 weeks until progression.

√ After off treatment following disease progression, physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 6 months until 3 years after registration.

Toxicity should be evaluated until resolution of any adverse events.

π After Cycle 3, 0 - 3 days prior to start of Cycle 4.

9.2 Arm 2 - Octreotide LAR depot + Interferon alpha-2b

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Ω	√
REQUIRED STUDIES	PRE	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Follow-Up Prior To	Follow-Up After
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	Progression	Progression
PHYSICAL ∑															
History and Physical Exam	X				X			X			X			X	X
Weight and Performance Status	X				X			X			X			X	
Blood Pressure	X														
Disease Assessment %	X										X			X	
Toxicity Notation		X			X			X			X			X#	X#
Baseline Abnormalities Assessment	X														
LABORATORY ∑															
CBC/Differential/Platelets/Hemoglobin	X				X			X			X				
Serum Creatinine	X				X			X			X				
UPC (urine protein creatinine) ratio	X														
Bilirubin	X				X			X			X				
SGOT or SGPT	X				X			X			X				
PT and PTT	X														
Albumin, calcium, glucose, alkaline phosphatase, LDH, electrolytes (Na, K, Cl, CO2, Mg) ß	X														
Serum chromogranin A, neuronspecific enolase, urinary 5HIAA ¶	X										X				

Calendar continued on next page. Click here for footnotes.

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Ω	√
REQUIRED STUDIES	PRE	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Follow-Up Prior To Progression	Follow-Up After Progression
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12		
SPECIMEN SUBMISSION															
Archived tissue per Section 15.2a (Required)	X														
Blood per Section 15.2b (Recommended)	X				X										
IMAGING PROCEDURES ∑															
CT (or MRI) for disease assessment %	X										X			X	
SPECT (octreotide scan) per Section 15.1b (Recommended)	X									Xp					
TREATMENT ∑															
Octreotide LAR depot		X			X			X			X				
Interferon alpha-2b £		X	X	X	X	X	X	X¥	X	X	X	X	X		

Note: Forms are found in Section 18.0. Forms submission guidelines are found in Section 14.0.

FOOTNOTES

∑ Protocol treatment and parameters will continue at these intervals until progression of disease or until patient has met any of the guidelines in Section 7.5.

% CT (or MRI) must be submitted for central radiology review (see Section 15.1 and Appendix 18.5). CT (or MRI) should be performed at baseline and every 9 weeks until progression using the same modality as the pre-study exam.

ß These tests are recommended for pre-study (see Section 7.1).

¶ These tests are required for pre-study and should be performed at the time of each disease assessment if elevated at baseline.

Ω After off treatment prior to disease progression, x-rays/scans for disease assessment and physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 9 weeks until progression.

√ After off treatment following disease progression, physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 6 months until 3 years after registration.

Toxicity should be evaluated until resolution of any adverse events.

£ Interferon alpha-2b to be given on Days 1,3,5,8,10,12,15,17,19 of each cycle.

¥ Optional. At the discretion of the treating investigator, patient may have a one-week break from interferon during the first week of every other cycle beginning with Cycle 3.

π After Cycle 3, 0 - 3 days prior to start of Cycle 4.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Measurability of lesions

a. **Measurable disease**: Lesions that can be accurately measured in at least one dimension by 1) medical photograph (skin or oral lesion), palpation, plain x-ray, CT, MRI or other conventional technique with longest diameter 2 cm or greater in the axial plane (bone lesions not included), or 2) spiral CT with longest diameter 1 cm or greater. Ultrasound is suitable only for superficial disease (superficial palpable nodes, subcutaneous lesions, thyroid nodules).

Helical/spiral CT images should be acquired using a slice thickness no more than 5mm (preferably 2 mm). Axial CT scanning cannot be used. MRI images should be acquired using a slice thickness no more than 7 mm. Refer to Appendix 18.5, Section 1.0 for CT and MRI guidelines.

b. **Non-measurable disease**: All other lesions including lesions too small to be considered measurable, pleural or pericardial effusions, ascites, bone disease, inflammatory breast disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed and followed by imaging techniques, cystic lesions or disease documented by indirect evidence only (e.g., by lab values), previously radiated lesions that have not progressed.

10.2 Objective status at each evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. All measurable lesions not identified as target lesions are non-target lesions and are included as non-measurable disease. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

a. **Complete Response (CR)**: Complete disappearance of all measurable and non-measurable disease. No new lesions. No disease related symptoms. Normalization of markers and other abnormal lab values. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR)**: Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of longest diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable**: Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of longest diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**: Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect objective status except in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR), and in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression.

6. Appearance or worsening of pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 CR/CR; and Relapse from CR or CRi

Best Response: This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	**DESCRIPTION**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	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	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Time to Treatment Failure

From date of randomization (which is the date of registration) to date of first observation of progressive disease (as defined in Section 10.2d), death due to any cause, symptomatic deterioration (as defined in Section 10.2e), or discontinuation of treatment. Patients last known not to have failed treatment are censored at date last known not to have failed.

10.6 Progression-Free Survival (Central-Review Based)

From date of randomization (which is the date of registration) to date of first documentation of progression based on Central Radiological Review of the appropriate CT or MRI scans, or symptomatic deterioration (as defined in Section 10.2e)), or development of new lesions or disease not identified on CT or MRI, or death due to any cause. Patients who have a local assessment of progression based on imaging, but for whom central review does not concur, will be censored at the last imaging date, unless subsequent scans or documentation of symptomatic deterioration provides evidence of progression. Patients last known not to have progressed are censored at the date of last contact.

10.7 Progression-Free Survival (Investigator Assessed)

From date of randomization (which is the date of registration) to date of first documentation of progression or symptomatic deterioration (as defined in Sections 10.2d and 10.2e), or death due to any cause. Patients last known not to have progressed are censored at date of last contact.

10.8 Time to Death

From date of randomization (which is the date of registration) to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

10.9 Tumor Marker Response (chromogranin A, neuronspecific enolase, urinary 5HIAA)

a. Objective status at each evaluation: For each tumor marker that is greater than the Upper Limit of Normal at prestudy, objective status is to be recorded at each evaluation.

1. Tumor Marker Partial Response: Greater than or equal to 50% reduction in baseline tumor marker level, or reduction to less than or equal to the Upper Limit of Normal.

b. Best Response: This is calculated from the sequence of objective statuses.

1. Confirmed Tumor Marker PR: Two or more objective statuses of Tumor Marker PR a minimum of four weeks apart documented before central-review based progression. Best response for objective disease must be stable/no response or better (see Sections 10.3a-e).

2. Unconfirmed Tumor Marker PR: One objective status of Tumor Marker PR documented before central-review based progression but not qualifying for confirmed Tumor Marker PR. Best response for objective disease must be stable/no response or better (see Sections 10.3a-e).

3. No Tumor Marker Response: Objective Tumor Marker status does not qualify as a Tumor Marker PR.

4. Inadequate Assessment, response unknown: When best response for objective disease is inadequate or unknown (see Section 10.3h) or when Tumor Marker has been inadequately assessed, then Tumor Marker Response will be coded likewise.

11.0 STATISTICAL CONSIDERATIONS

11.1 Primary Objective

The primary objective is to compare central review-based progression-free survival (PFS) in patients with advanced, poor prognosis carcinoid cancer treated with octreotide plus either interferon or bevacizumab. Based on historic experience, it is assumed that the median progression-free survival in the octreotide/interferon group of patients will be 6 months, and that an improvement of 50% (a hazard ratio of 1.5, corresponding to an improvement to a median of 9 months) would be of clinical interest. Prior to the first

interim analysis it was noted that the event rate was lower than originally hypothesized, and was more consistent with approximately 15 months. Thus, the originally proposed hazard ratio of 1.5 would correspond to a median of 22.5 months, a difference of 7.5 months. It was determined that a hazard ratio of 1.4 (corresponding to a median of 21 months) would be of clinical interest. This hazard ratio is also consistent with differences from 12 to 16.6 months, or 18 to 25.2 months, depending on the actual final number of central-review PFS events are in the control arm.

11.2 Accrual and Power Justification

Assuming an additional year of accrual (from 3 to 4 years), and a total of two years of follow-up after the end of accrual, 400 eligible patients will be sufficient to detect a 1.4 hazard ratio with >84% power (depending on the final control arm hazard rate), based on a two-sided .05 level test. Assuming a 6% cushion for ineligible patients, the total accrual is estimated to be 424 total patients.

11.3 Analyses

Overall survival, time to treatment failure, traditionally reported progression-free survival, objective response and toxicity will be evaluated as secondary endpoints.

According to the intent-to-treat principle, all eligible patients will be included in the analyses according to the randomized treatment assignment, regardless of actual treatments received. Central-review based progression-free survival is the primary endpoint, and will be analyzed using the stratified log rank test (which is the score test from the stratified Cox-model) using stratification factors as defined in Section 6.0. Overall survival will be analyzed in a similar fashion. For the secondary endpoint of response, the analyses are conducted in the subset of patients with measurable disease according to the randomized treatment assignment. This endpoint will be analyzed using a logistic regression model.

11.4 Central-Review Board Based Progression

For this study, the assessment of progression based on increase in imaged tumor size will be centrally assessed by ACRIN. Date of disease assessment and determination of progression will be forwarded to the SWOG Statistical Center, and compared with progression determinations reported by the local investigator. The actual progression time will then be determined at the Statistical Center using the minimum time from the date of randomization (which is the date of registration) to either this reviewed progression date, or to the date of symptomatic deterioration, development of new lesions, or other documentation of disease, or death. This will constitute the primary study endpoint, and will be used in all interim analyses

11.5 Toxicity Reporting and Analysis

Toxicities will be graded according to the NCI CTCAE (Common Terminology Criteria for Adverse Events) Version 3.0 for routine toxicity reporting and according to NCI CTCAE Version 4.0 for Serious Adverse Event (SAE) reporting. Eligible patients who did not receive any protocol treatment will not be included in the toxicity analysis.

11.6 Interim Analysis

Interim analysis: In addition to regular study monitoring, there will be three formal interim analyses. The first will be done after approximately 90 actual events (scheduled to correspond with the timing of the original study design). Under the null hypotheses, and the assumption that the true median in the control arm is 15 months, this will occur when approximately 26% of the expected number of CRb-PFS events have occurred. The remaining two interim analyses will occur when approximately 50% and 75% of the expected events will occur, corresponding to approximately 180 and 270 events respectively. Evidence suggesting early stopping would be if the null hypothesis of no -difference or the alternative hypothesis of a 40% improvement is rejected using a 2-sided .005 level. Assuming the study continues to final analysis, the study will be analyzed when approximately 350 central review based progression-free survival endpoints have been observed (or after maximum of 4 years after the close of follow-up, whichever comes first) using a 2-sided level of .045 to account for the interim analyses.

The estimated number of events for these analyses is based on the assumption that PFS follows an exponential distribution, and that tumor assessments for the central review endpoint continue past local determinations of progression. Although the protocol dictates treatment until progression, the decision is based on local physician actions, not

the central reads. Institutions are instructed to continue tumor assessments after locally determined progression, but this may not be uniformly followed, causing potential for missing determinations of progression by central review. Thus, in addition to the analysis of the primary CRb-PFS, analyses will include sensitivity analyses, to evaluate the impact of potential incomplete tumor evaluations after locally determined progression. These analyses would include 1) using time to treatment failure, where a failure is progression based on central read, or removal from protocol treatment for other causes; 2) using time to earliest PFS event, whether based on central review or local; 3) censoring CRb-PFS at the time of last tumor assessment; and 4) analysis using the local determination of PFS. Because we are not able to determine apriori the impact of these different analyses, a final determination of the relative treatment effects will depend on how similar or different the results are in these analyses.

In addition to the analyses outlined above, comparisons between the CRb-PFS and traditionally reported PFS will be reported to the DSMC, so that any potential discrepancies between arms in the differences in these determinations may be reviewed.

11.7 Translational Medicine Analyses

We will assess the relationship of the expression profile of VEGF-A, -B, -C, -D, VEGFR -1, -2, -3, NRP-1, -2 and progression-free survival. A key aim will be to assess whether expression of a specific VEGF-receptor will predict patients who may benefit from therapy with bevacizumab. In statistical terms, this hypothesis corresponds to the presence of a treatment interaction in a proportional hazards model. We estimate that we will have specimens from approximately 85% of the patients available for analysis. Assuming 340 specimens, and roughly a 50:50 split between patients positive and negative for a specific marker, we will have 82% power to detect an interaction hazard ratio of 2.0 or greater (level .05 two sided). This calculation does not account for the presence of multiple tests, and thus interpretations of these analyses will need to be made with caution. In addition, we will perform logistic regression analyses to correlate expression profiles with tumor response.

We will also explore differences between treatment arms in tumor marker response of 5HIAA, chromogranin A and neuronspecific enolase among patients with elevated levels at baseline. We anticipate that approximately 80% of patients will have elevated 5HIAA at baseline, 70% will have elevated chromogranin A, and 50% will have elevated neuronspecific enolase. Assuming that we receive follow-up levels on 90% of these patients, we will have approximately 280, 250 and 180 patients respectively for the analysis of these markers. This number is sufficient to have 84% power to detect a difference of 15% in 5HIAA response (corresponding to 20% marker response in patients treated in the bevacizumab arm compared to 35% in the interferon arm) assuming a two-sided .05 level test. For chromagranin A we would have 84% power to detect a 13% difference (from 5% to 18%) and for neuronspecific enolase we would have 80% power to detect a 15% difference (5% to 20%). If the true differences are of smaller magnitudes than these values, our comparisons will be more exploratory in nature.

11.8 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of SWOG, three SWOG members, two non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

12.1 Pathology Review

All patients will undergo central pathology review. The purpose of this review is to confirm diagnosis. Instructions for submitting tissue are located in Section 15.2a.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than three working days prior to planned start of treatment).

13.2 Registration Requirements

For either phone or web registration, the individual registering the patient must have completed the appropriate SWOG Registration Form. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

The individual registering the patient must also be prepared to provide the treating institution's name and ID number in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base. Patients will not be registered if the IRB approval date has not been provided or is > 365 days prior to the date of registration.

13.3 Registration procedures

a. You may register patients from Member, CCOP and approved Affiliate institutions to a therapeutics study using the SWOG Registration program. To access the Registration program go to the SWOG Web site (http://swog.org) and click on the Logon link to go to the SWOG Members Area logon page (https://swog.org/visitors/logon.asp). This Web program is available at any time except for periods listed under Down Times. Log on as an Individual User using your SWOG Roster ID Number and individual web user password. Help for the logon process may be found at https://swog.org/visitors/logonhelp.asp. After you have logged on, click on the Clinical Trials link and then the Patient Reg link to go to the Entry Page for the Patient Registration program. If you are a Registrar at an institution with Internet access you are encouraged to register this way. For new users, the link to a "Starter Kit" of help files may be found by clicking on Starter Kit link at the logon page.

To register a patient the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,

2. You are associated as an investigator or CRA/RN to the institution where a registration is occurring, and

3. You are granted permission to use the Patient Registration program at that institution.

For assistance with points 1 and 2 call the SWOG Operations Office at 210/614-8808. For point 3 you must contact your Web User Administrator. Each SWOG institution has one or more Web User Administrators who may set up Web Users at their institution and assign permissions and passwords to these users. For other password problems or problems with the Patient Registration program, please e-mail webreghelp@crab.org. Include your name, Roster ID Number, and telephone number, when the problem occurred, and exactly what you were doing.

b. If the Web Reg program is not used, the registration must be done by phone.

Member, Affiliate and CCOP Institutions

Registration by phone of patients from member, affiliate and CCOP institutions must be done through the SWOG Data Operations Center in Seattle by telephoning 206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays.

13.4 Exceptions to SWOG registration policies will not be permitted

For either method of registration, exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

NOTE: CTSU institutions should refer to Appendix 18.7.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for ALL patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Form) must be submitted to the Data Operations Center in Seattle. Data from approved SWOG institutions must be submitted on-line via the Web; see Section 14.3a for details. Exceptions to online data submission are patient-completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports).

14.3 Data Submission Procedures.

a. SWOG institutions must submit data electronically via the Web by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on, click on the CRA Workbench link to access the home page for CRA Workbench website. Next, click on the Data Submission link and follow the instructions. For new users, the link to a "Starter Kit" of help files may be found by clicking on the Starter Kit link at the Members' logon page.

To submit data via the web the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/450-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page). For other difficulties with the CRA Workbench, please email *technicalquestion@crab.org*.

b. If you need to submit data that are not available for online data submission, the only alternative is via facsimile. Should the need for this occur, institutions may submit data via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use cover sheet for faxed data. Please make sure that each page of all faxed data include the SWOG patient ID, protocol number (**S0518**), and patient initials.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION:

Submit the following:

S0518 Prestudy Form

Baseline Tumor Assessment Form

S0518 Baseline Abnormalities Form

S0518 Hypertension Status Form

Pathology Report (NOTE: This is to be submitted to the Data Operations Center in Seattle. This submission is in addition to the pathology report submission to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division that is required by Section 15.2.)

For patients with disease progression after initial diagnosis (see Section 6.0b), submit a radiology report dated within 6 months of registration to support this designation.

Send baseline CT (or MRI) images to ACRIN (see Appendix 18.5). (Required)

Send baseline SPECT (Octreotide Scan) imaging and data form to ACRIN (see Appendix 18.6). (Recommended)

b. WITHIN 30 DAYS OF REGISTRATION:

Submit archived tissue for pathology review as per Section 15.2a. (Required)

c. IMMEDIATELY FOLLOWING PRE-TREATMENT AND WEEK 4 BLOOD DRAWS:

Submit blood for translational medicine studies as per Section 15.2b. (Recommended)

d. AFTER EVERY CYCLE WHILE ON PROTOCOL TREATMENT (NOTE: 1 CYCLE = 21 DAYS):

Submit the **S0518** Treatment Form and **S0518** Adverse Event Form. Also submit the **S0518** Hypertension Status Form, if applicable.

e. AFTER EVERY TUMOR ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF TREATMENT PRIOR TO DISEASE PROGRESSION):

Submit the Follow-Up Tumor Assessment Form.

Submit the **S0518** Tumor Markers Reporting Form.

Send CT (or MRI) images to ACRIN (see Appendix 18.5). (Required)

Send Week 9 SPECT (Octreotide Scan) imaging and data form to ACRIN (see Appendix 18.6). (Recommended)

f. WITHIN 14 DAYS OF PROGRESSION:

Submit the Follow-Up Tumor Assessment Form and either:

Follow Up Form (if patient is off treatment at time of progression)

OR

S0518 Treatment Form and **S0518** Adverse Event Form (if patient is still on protocol treatment)

g. WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

Submit the following:

S0518 Treatment Form

S0518 Adverse Event Form

S0518 Hypertension Status Form, if applicable

Off Treatment Notice

h. EVERY 6 MONTHS AFTER OFF TREATMENT UNTIL DEATH OR 3 YEARS AFTER REGISTRATION:

Submit the Follow Up Form.

i. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death and either:

S0518 Treatment Form and **S0518** Adverse Event Form (if the patient was still on protocol treatment)

OR

Follow Up Form (if the patient was off protocol treatment) documenting death information

NOTE: CTSU institutions should refer to Appendix 18.7.

15.0 SPECIAL INSTRUCTIONS

15.1 Radiology Review

CT, MRI and SPECT images will be initially interpreted by the local site radiologist. Imaging exams will then be forwarded to American College of Radiology Imaging Network (ACRIN) in Philadelphia for central review.

a. CT/MRI Imaging

All CT and/or MRI images must be submitted to ACRIN for central review.

All study participants will have a CT or MRI exam prior to study entry. Participants will then undergo additional imaging every 9 weeks until progression of disease. The same imaging modality used for the pre-treatment exam must be used for the post-treatment exams (i.e., patients with a pre-study CT are to receive follow-up CT scans throughout the trial for assessment of progression; participants with a pre-study MRI are to receive follow-up MRI scans throughout the trial for assessment of progression). Each CT/MRI should be performed per Appendix 18.5, Section 1. ACRIN will perform a central/expert review per RECIST criteria; the central review-based PFS is the basis for the primary endpoint, as identified in Section 11.0. Real-time assessment and feedback of the central radiology review is not feasible, therefore, clinical management and treatment decisions will be made by the treating physician based on local site assessments and other clinically appropriate considerations. Results of the central review will only be reported to the DSMC. A detailed description of the central radiology PFS review, including CT/MRI acquisition parameters and image submission instructions, can be found in Appendix 18.5.

b. SPECT Imaging - Octreotide Scan

Institutions are required to seek additional patient consent to submit octreotide scans. If consent is granted, patient must be registered to Registration Step 2 (see Sections 5.2a-5.2b).

A number of participants will undergo SPECT imaging as part of their standard clinical management. If SPECT imaging is performed, study sites are asked to submit 2 SPECT scans: a baseline SPECT **(performed within 28 days prior to Registration Step 1)** and a SPECT scan performed after the third treatment cycle. Each SPECT scan should be performed using the acquisition parameters per Appendix 18.6. The SPECT scans are to be sent to ACRIN for central review. ACRIN will perform a central review to assess the exploratory aims indicated in Appendix 18.6. Clinical management and treatment decisions will be made by the treating physician based on local site assessments and other clinically appropriate considerations. A detailed description of the SPECT sub-study, including acquisition parameters and image submission instructions, can be found in Appendix 18.6.

15.2 Specimen Submission

Specimens for pathology review, correlative studies and banking (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201):

a. Specimens must be submitted at the following timepoint for pathology review (see Sections 9.1 and 9.2):

1. Submit tumor bearing block (preferred) within 30 days of registration. If tumor block cannot be sent, send 10 unstained slides of representative tumor section. Pathology report must be sent with specimen.

   NOTE: This will be used for pathology review (see Section 12.1). With additional patient consent, this tissue will also be used for the VEGF testing described in Appendix 18.2. With further consent, any specimens not consumed by testing specified in this protocol will be retained in the SWOG bank for future unspecified testing.

b. With patient's consent specimens must be submitted at the following times (see Sections 9.1 and 9.2):

   1. 2 EDTA tubes of blood after registration prior to treatment and on Cycle 2 Day 1 prior to treatment.

      NOTE: With additional patient consent, remaining tissue will be stored until funding is obtained to perform the studies described in Appendix 18.2. With further consent, any specimens not consumed by testing specified in this protocol will be retained in the SWOG bank for future unspecified testing.

c. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp), or via the link on the **S0518** protocol abstract page on the SWOG website (www.swog.org).

d. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

For each investigational drug supplied for a study, drug disposition (drug receipt, dispensing, transfer or return) shall be maintained on the NCI Investigational Drug Accountability Record. Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the Drug Accountability Record; the SWOG ID # and initials of the subject to whom drug is dispensed, the dose, the date(s) and quantity of drug dispensed to the subject, the date(s) and quantity of drug returned to the NCI or transferred to another NCI-approved protocol, the balance forward, lot number and recorder's initials. These Drug Accountability Records must be readily available for inspection and are open to FDA or NCI inspection at any time.

Publication and Industry Contact

The agent (hereinafter referred to as "Agent"), bevacizumab, used in this protocol is provided to the NCI under a Clinical Trials Agreement (CTA) between Genentech (hereinafter referred to as "Collaborator") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines apply to the use of the Agent in this study:

1. Agent may not be used outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Collaborator data for Agent are confidential and proprietary to the Collaborator and should be maintained as such by the investigators.

2. For a clinical protocol where there is an investigational Agent used in combination with another investigational Agent, each the subject of different CTAs or CRADAs, 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 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 which 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 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. The NCI encourages investigators to make data from clinical trials fully available to Collaborators for review at the appropriate time (see #5). The NCI expects the clinical trial data developed under a CTA or CRADA will be made available exclusively to Collaborator, and not to other parties.

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 the Collaborator 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 should be provided to CTEP for immediate delivery to the Collaborator for advisory review and comment prior to submission for publication. Collaborator will have 30 days from the date of receipt for review. An additional 30 days may be requested in order to ensure that confidential and proprietary data, in addition to the Collaborator's intellectual property rights, are protected. Copies of abstracts should be provided to the Collaborator for courtesy review following submission, but prior to presentation at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to:

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   Executive Plaza North, Room 7111
   Bethesda, Maryland 20892
   FAX: 301/402-1584

   The Regulatory Affairs Branch will then distribute them to the Collaborator.

Monitoring

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.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also Appendix 18.3 for general and background information about expedited reporting.

b. Reporting methods

This study requires that expedited adverse event reporting use the NCI's Adverse Event Reporting System (CTEP-AERS). The NCI's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. An CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS web-based application located at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in Table 16.1 or 16.2, as applicable.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Any supporting documentation requested by CTEP should be submitted in accordance with instructions provided by the CTEP-AERS system.

d. Other recipients of adverse event reports

The Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable must also be reported according to local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

e. Expedited reporting for investigational arm

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent(s) used in this study is bevacizumab. An adverse event occurring in the bevacizumab/octreotide arm, whether attributable to bevacizumab or octreotide, should be reported using the same expedited reporting guidelines. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:
Phase II and III Trials Utilizing an Agent under a CTEP IND CTEP-AERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days[1] of the Last Dose of the Investigational Agent bevacizumab in this Study

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

f. **Expedited reporting for commercial arm**

Commercial reporting requirements are provided in Table 16.2. The commercial agents used in this study are interferon alpha and octreotide. If there is any question about the reportability of an adverse event, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.2. Expedited reporting requirements for adverse events experienced by patients on this study who have received the commercial drug(s) listed above.

ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted using the CTEP-AERS system Commercial Drug pathway within 7 working days of learning of the event.

a This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

g. Reporting secondary AML/MDS

1. All cases of acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following chemotherapy for cancer must be reported in CTEP-AERS.

   i. In protocols using CTCAE Version 4.0 for SAE reporting, three options are available to describe treatment-related events:

   - Leukemia secondary to oncology chemotherapy
   - Myelodysplastic syndrome. NOTE: The only grading option for "Myelodysplastic syndrome" is Grade 4, life-threatening. If reporting MDS that is other than Grade 4, use “Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, (specify,__)” and insert MDS as the specify term.
   - Treatment related secondary malignancy

   ii. In protocols using CTCAE Version 3.0 for SAE reporting, the event(s) can be reported as “Secondary malignancy-Other (specify, ___)”. Report MDS as “Myelodysplasia,” in the BLOOD/BONE MARROW category.

   iii. Secondary malignancies other than AML/ALL/MDS that are related to protocol treatment must also be reported in CTEP-AERS.

iv. Non-treatment related cases of AML/ALL/MDS must be reported as follows:

In protocols using CTCAE Version 4.0 for SAE reporting, report as “Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify”

In protocols using CTCAE Version 3.0 for SAE reporting, report MDS as “Myelodysplasia” and Leukemias as “Blood/Bone Marrow - Other (Specify, __)”

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

2. The following supporting documentation must also be submitted within 30 days:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

Submit the Report and documentation to:

SWOG
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

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18.0 APPENDIX

18.1 New York Heart Association

18.2 Translational Medicine Laboratory Methods

18.3 Determination of Expedited Adverse Event Reporting Requirements

18.4 Self-Administration of Interferon

18.5 Central Radiology Review

18.6 SPECT (Octreotide Scan) Study

18.7 CTSU Participation Procedures

18.1 New York Heart Association

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, & 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.

18.2 Translational Medicine Laboratory Methods

Specimens from this study will be stored until funding is obtained to pay for the following tests.

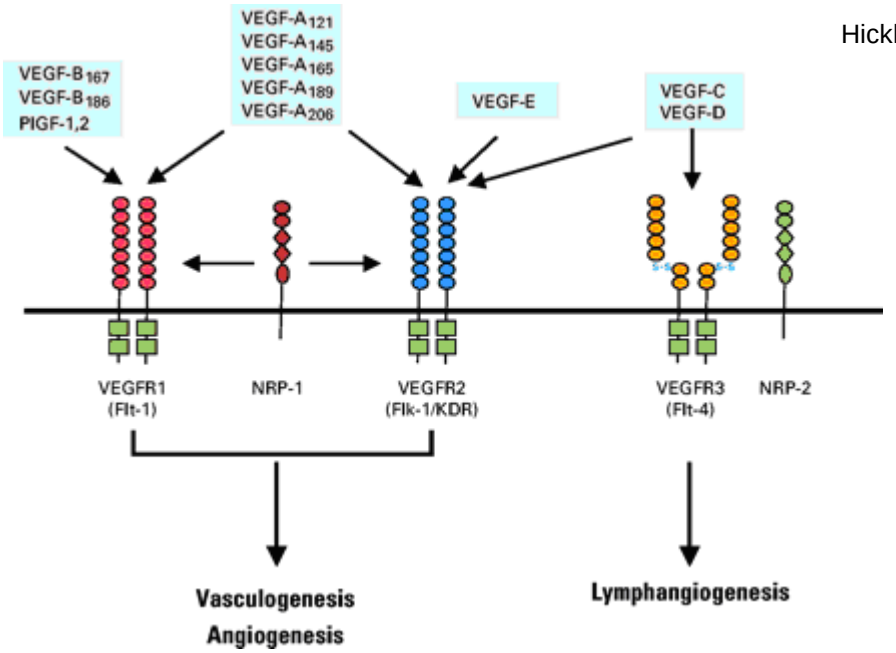
Expression profile of VEGF species and receptor subtypes in carcinoid tumor tissue and its relationship to outcome

Residual carcinoid cancer tissue from surgical resection or biopsy will be collected for analyses. Based on the Phase II experience with bevacizumab in carcinoid, we estimate that residual carcinoid tumor tissue will be available in 85% of accrued patients. Thus, we estimate that approximately 241 specimens will be banked and be available for analyses.

Tumor tissue will be sectioned into 5 micron slices and mounted onto glass slides. Standard immunohistochemical procedures will be used to stain tumor material for expression of VEGF-A, -B, -C, -D, VEGFR -1, -2, -3, NRP -1, -2.

Preliminary studies using specimens collected during the Phase II trial are ongoing. Reagents and assay methodology will be established and evaluated for their specificity, sensitivity and reproducibility prior to the consumption of material from the Phase III trial. Banked specimens will also serve as a repository for future studies.

Hicklin, D. J. et al. *(27)*



The Phase II study has served to demonstrate that therapy targeting VEGF is promising in neuroendocrine carcinoma. It is one of few malignancies that has demonstrated tumor shrinkage from antiangiogenic therapy without addition of cytotoxic agents. Nonetheless, therapy with bevacizumab does not result in cure of the disease. A number of patients who initially clearly benefited from treatment later had disease progression. This proposed Phase III trial will serve as a unique venue for investigating the biology of the VEGF pathway.

Studies have shown that VEGF-A, -B, -C, and -D can signal through a variety of receptors. *(27)* VEGFR -1, -2, -3 have tyrosine kinase activity. NRP -1, -2 may bind either VEGF or semaphorin and may act through alternative pathways. Currently therapy targeting VEGF pathway targets either the ligand or the receptor tyrosine kinases.

Bevacizumab binds the ligand VEGF A only and may thus interfere with signaling through VEGFR -1, -2 as well as NRP -1, -2 pathways. Bevacizumab does not inhibit signaling through VEGFR -1, -2, -3 mediated by PIGF -1, -2, VEGF-B, -C, -D. Current VEGF receptor tyrosine kinase inhibitors block signaling through VEGFR-1, -2 (and -3 in some cases). They do not block VEGF-A, -B, and -C triggered signaling through NRP -1, -2.

Signaling through VEGFR-1, and -2 is linked to angiogenesis, which may serve to sustain tumor growth. Signaling through VEGFR-3 by VEGF-C, -D is linked to lymphangiogenesis and distant lymph node metastasis in human malignancies.

In addition the expression of VEGF receptors in the stroma of neuroendocrine tumors, VEGFR-1, -2, NRP -1, -2 have also been reported to be expressed on carcinoid tumor cells. *(6,28,29)* Molecular abnormalities in the VEGF pathway have also been described in neuroendocrine carcinoma. Chromosome 11q13 is the site of both the MEN1 and VEGF-B gene. *(30,31)* This region of chromosome 11 is frequently deleted in both familial as well as sporadic neuroendocrine tumors of lung, thymus, pancreas, and proximal gastrointestinal tract. NRP-2 appears to be expressed in normal neuroendocrine cells lining the digestive tract. Loss of expression has been reported in carcinoid tumors arising from the appendix, colon, and rectum. *(32)*

Therefore, we expect the expression profile of VEGF family members and their receptors may predict who will benefit from therapy with bevacizumab, a monoclonal antibody against VEGF-A. The relationship between sites of metastasis and pattern of VEGF expression will also be analyzed.

Relationship between blood angiogenic markers and clinical outcome in carcinoid patients undergoing anti-angiogenic therapy

As an optional procedure for this trial, patients will be asked to have 8 cc blood collected at baseline and 3 weeks after treatment. Blood will be separated for plasma and cells. It will be stored at a central lab for batched analyses. Based on our experience with multiple Phase II trials, we expect greater than 90% participation.

We plan to measure blood products of nitric oxide metabolism, which is an important regulatory molecule for vascular function and critical mediator of VEGF/VEGFR signaling. *(33)*

Preliminary studies using specimens collected during the Phase II trial are ongoing. Reagents and assay methodology will be established and evaluated for their specificity, sensitivity and reproducibility prior to the consumption of material from the Phase III trial. Banked specimens will also serve as a repository for future studies.

The Phase II trial with bevacizumab in carcinoid tumors demonstrated rapid decrease in tumor blood flow, blood volume and permeability surface area within 48 hours of the first dose of bevacizumab. Therapy was also associated with a high rate of Grade 3-4 hypertension. The rate of Grade 3-4 hypertension observed in the carcinoid trial (CTCv3 53%; unpublished data presented at ASCO 2005) was significantly higher than those observed in colon cancer (11%) and renal cell carcinoma (21%) trials. Hypertension, for some patients, is a dose limiting toxicity leading to the withdrawal of treatment in patients clinically benefiting from therapy. It is likely that the rapid decrease in tumor blood flow and hypertension are due to factors other than trimming of tumor blood vessels. We hypothesize that neutralization of circulating VEGF may result in down regulation of Nitric Oxide (NO) production resulting in vasoconstriction, decreased tumor blood flow, and hypertension.

Bevacizumab is a humanized IgG against VEGF-A. In previous studies, following therapy with bevacizumab, levels of circulation free VEGF-A were below the limits of detection. Preliminary data from the current Phase II trial have also shown decrease in plasma VEGF in a portion of patients treated with interferon. We expect with therapy there will be a decrease in the level of circulation free VEGF-A correlating with changes in level of NO, degree of hypertension, and may predict clinical benefit from therapy.

Assuming 90% participation in this part of the study, we will have paired specimens on 255 patients. We will explore the distribution of changes in Nitric Oxide production between baseline and post-treatment specimens. Of specific interest will be to assess the impact of these changes on progression free survival using the proportional hazards model. Our initial explorations of the distributions of these changes will determine whether absolute differences, or some categorized summary of the changes between baseline and post-treatment will be used in the analyses. As in the section above, we will want to assess whether changes in NO differ by treatment group, and how such differences affect outcome. In addition, we will assess the impact of these levels on tumor response and risk of Grade 3-4 hypertension using logistic regression.

18.3 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.0.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration*: When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration*: When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm, but the commercial agent(s) is given for a period of time prior to starting the investigational agent(s), expedited reporting of adverse events that occur prior to starting the investigational agent(s) would follow the guidelines for commercial agents. Once therapy with the investigational agent(s) is initiated, all expedited reporting of adverse events should follow the investigational guidelines.

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

Step 1: Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov). Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: *Grade the event using the NCI CTCAE version specified.*

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event. Expected* events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected,* for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in

- the current NCI Agent-Specific Adverse Event List (for treatments using agents provided under an NCI-held IND);
- the drug package insert (for treatments with commercial agents only);
- Section 3.0 of this protocol.

Step 5: *Review Tables 16.1 and 16.2 in the protocol to determine if there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included an investigational agent(s), a commercial agent(s), or a combination of investigational and commercial agents.*

NOTE: If the patient received at least one dose of investigational agent, follow the guidelines in Table 16.1. If no investigational agent was administered, follow the guidelines in Table 16.2.

NOTE: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the agent(s) must be reported according to the instructions in Table 16.1.

18.4 Self-Administration of Interferon

Patients deemed competent to self-administer the interferon may do so. The hospital or clinic staff will instruct the patient or interested family member in this technique. Patients should be allowed to administer these injections at home when they can independently perform a return demonstration for their instructor. The instructor will note this fact in the patient's record. Adequate contact persons and telephone numbers will be provided so that the patient will always be able to reach someone familiar with this procedure should they need assistance.

Instructions for Self-Administering Medication

1. Preparation

   a. Wash hands well. Take acetaminophen (Tylenol®) as premedication if directed by your doctor.

   b. Assemble necessary supplies. The Interferon should be kept refrigerated until several minutes before each treatment. You also need a syringe with a needle, at least 3 alcohol prep pads, and a container* for used materials.

      _____

      *An unbreakable, leak-proof, reclosable container - milk carton, coffee can.

2. Reconstituting the Interferon Powder

   a. If this is the first dose that will be coming from a vial, the Interferon powder must be dissolved, using the diluent provided. Snap the plastic cap off both vials, and cleanse both rubber stoppers with an alcohol pad and allow to air dry.

   b. There may be a different syringe/needle provided that you will use to reconstitute the Interferon. Open the package containing one of these syringes and attach (or tighten) the appropriate needle to it. Pull back the plunger of the syringe so that the top of it rests right on the line representing the volume of diluent that you are to add to the Interferon powder.

   c. Insert the needle through the stopper of the diluent vial, and invert the vial/syringe in front of you at eye level, holding the syringe in your dominant hand and the vial in the other.

   d. Inject the air from the syringe into the vial slowly. If you feel like you are forcing it, pull back the plunger to allow some solution into the syringe, then push the remaining air into the vial. Ultimately, your syringe should be filled with diluent solution up to the correct line and no air will be left in the syringe. If you have bubbles, tap the syringe with your finger until they rise to the top, push them up into the vial and recheck the plunger to insure that it is still at the correct volume mark.

   e. Withdraw the needle from the diluent vial and insert it into the vial containing the Interferon powder. This time keep the vial on the surface and push the plunger down to inject the diluent into the powder vial. If you meet resistance, allow some air to rise into the syringe before pushing down and expelling the remaining solution into the vial.

Eventually, all the solution will be in the vial. Pull back the plunger to return it to the line that is the same as the volume of solution that you injected. This will prevent pressure build-up in the Interferon vial. Remove the needle and discard it appropriately.

f. To help dissolve the Interferon powder, you may need to roll the vial between your palms or swirl the solution around. DO NOT shake the vial. Be sure that all the powder is dissolved before proceeding to #3.

3. Withdrawing Your Dose From the Vial

a. Cleanse the rubber stopper of the vial containing the Interferon solution with an alcohol pad and allow to air dry.

b. Open syringe package and needle package (if separate) and attach or tighten needle by twisting until tight. Pull back the plunger to the mark that represents your dose (i.e., 3 mU/0.5 ml, top of plunger should rest at the 0.5 ml mark). This fills the syringe with air in a volume equal to the volume of your dose.

c. Uncap the needle and push it through the stopper, at least half-way into the vial. Now pick up the vial (with syringe/needle in it) with your left hand and turn it upside down, holding it at eye-level, about 12 inches from your face. You should now have the vial in one hand and your other hand free to manipulate the syringe. (Note: Left-handed persons should have the vial in their right hand, so that they can manipulate the syringe with their left hand.)

d. Inject air from the syringe into the vial slowly, and then withdraw the plunger. The syringe will gradually fill with drug solution. Repeat this procedure until only solution is in the syringe, solidly, to the mark that indicates your dose. Withdraw needle and recap it.

4. Administration

a. Thoroughly clean the area to be injected with an alcohol pad. Areas appropriate for this type of injection have been shown to you. A new site should be used for each injection whenever possible.

b. As demonstrated, pinch 1 1/2 to 2 inches of loose skin from the site to be injected.

c. Uncap the needle, and insert the needle approximately 1/4 inch into the skin and push the syringe plunger in all the way, thereby giving the dose of Interferon.

d. Remove needle and wipe injection site with a new alcohol pad, but do not massage the area to any great extent.

e. Carefully recap needle and return needle and syringe to the clinic pharmacy for disposal. If the Interferon vial contains more than one dose, write the date on the label. It is usable for 30 days.

f. If a drug administration diary has been provided, remember to complete it after each dose. Enter the date and time of day given, along with any notable side effects that you may have experienced since the previous dose was given.

18.5 Central Radiology Review

Note: Due to the rarity of this disease (advanced/poor prognosis carcinoid) and the need to enroll participants from a large number of sites, ACRIN will not require participating SWOG sites to undergo the standard site qualification and approval process.

All participants will undergo serial CT or MRI imaging:

- Baseline/pre-treatment: performed within 28 days prior to registration.
- Every 9 weeks until progression of disease (as determined by local site assessment)

The same imaging modality MUST be used throughout the course of the trial. The pre- and post-treatment CT or MRI images must be submitted to ACRIN for all study participants. Imaging guidelines and image submission instructions are detailed below.

Since real-time assessment and reporting of the central radiology review is not feasible, clinical management and treatment decisions will be made by the treating physician based on local site assessments and other clinically appropriate considerations.

1.0 Image Acquisition

All study participants will undergo serial CT or MRI imaging to be done at baseline (performed within 28 days prior to registration) and every 9 weeks until progression of disease (as determined by local site assessment).

1.1 CT Imaging

General CT imaging parameters are outlined below. Additional scanning guidelines, per anatomic location, are detailed in the subsequent sections (1.1.1 – 1.1.3).

- Helical CT scanning is required; axial scanning cannot be used.
- Multi-detector scanning is preferred whenever possible, but single-detector helical scanning can be used.
  - Single detector scanners: Pitch should be 1-1.5; images should be reconstructed at ≤ 5mm intervals in the axial plane.
  - Multi-detector scanners: It is strongly recommended that reconstruction be performed at the highest resolution possible (2 mm or less), but will accept ≤ 5mm intervals.
- Each anatomic area (chest, abdomen, pelvis), scanner settings (kV, mAs) should be per institutional routine procedures.
- Choice of contrast agent should be according to local institutional routine.
- Contrast dose should be 100-150 mL.
- Injection rates should be 2 mL/sec minimum for chest and pelvis imaging and 3-5 mL/sec for abdominal imaging.
- 18G IV is preferred for bolus rates of injection, especially for abdominal imaging.
- Central lines should not be used unless absolutely required due to lack of acceptable peripheral IV access. Central lines should not be used with power injector unless specifically approved for that indication.

1.1.1 Abdominal CT

As the vast majority of metastatic lesions in carcinoid tumor occur in the liver, it is expected that abdominal scanning will be performed in all participants at all time points. Even if there is no documented liver disease at the time of enrollment, abdominal imaging with a multi-phase scanning technique should be performed prior to enrollment in order to exclude the presence of hypervascular lesions occult to other (non-dynamic) scanning procedures. Even if pre-enrollment multi-phase contrast scanning of the abdomen fails to demonstrate hepatic metastatic disease, abdominal imaging should be performed at all subsequent time points to exclude disease progression through the appearance of new hepatic metastases.

Abdominal imaging should be tailored for multi-phase liver imaging techniques. Pre- and post-IV contrast imaging provides optimal evaluation of liver disease; IV contrast should be used whenever possible. In cases when there is a contraindication to IV contrast, MRI is the preferred imaging modality for liver disease (if available).

Recommended scanning protocol: Helical non-contrast imaging through the liver prior to contrast-enhanced imaging, followed by dual-phase (arterial and portal) contrast enhanced imaging is recommended. Arterial phase scan delay time 20-30 seconds (or via bolus timing techniques per institutional routine). Portal venous scan delay time approximately 60-75 seconds. Each vascular phase scan of the liver must be obtained in a single helical acquisition.

1.1.2 Pelvic CT

Pelvic imaging will be employed as part of total abdominal and pelvic imaging. The abdominal (liver) protocol should be used with the pelvic imaging to follow, preferably during the late portal phase (approximately 80-90 seconds after injection) as to preserve the multi-phase abdominal (liver) imaging protocol.

1.1.3 Chest CT

Chest imaging will be performed if the patient has or is suspected to have involvement of disease in the chest at baseline. If documented chest disease involvement, all subsequent imaging will include chest CT scans. For assessment of chest disease, CT scanning is preferred. However, if MRI is utilized for evaluation of target liver lesions and chest imaging is also required for assessment of non-target lesions, chest MRI may be performed (see Section 1.2.). Scanning with IV contrast is preferred, but not required. If IV contrast is used, pre-contrast imaging is not required. Chest CT scanning should be performed per institutional standards, as long as slice resolution requirements are met ($\leq$ 5mm, preferably $\leq$ 2mm). For contrast-enhanced imaging, a scan delay of approximately 20-30 seconds is recommended. If chest imaging is combined with abdominal (and pelvic) imaging, chest imaging should either be performed prior to abdominal imaging (non-contrast chest) or after abdominal (and pelvic) imaging.

1.2 MRI Imaging

General MRI imaging parameters are outlined below. Additional scanning guidelines, per anatomic location, are detailed in the subsequent sections 1.2.1 – 1.2.3.

- Field strength of 1 tesla or greater.
- Imaging must be performed with a specialized torso array coil or other local coil combinations appropriate for body imaging. Body coil for signal reception is not acceptable.
- Image slice thickness should be $\leq$ 7 mm.
- For contrast enhanced scanning, standard gadolinium chelates should be used at a dose of 0.1 mmol/kg to a maximum of 20mL.
- Injection rate should be 2cc/sec, and all injections must be followed by a saline flush of at least 20cc. Peripheral 22-20G IV preferred.

1.2.1 Abdominal MRI

Contrast enhanced imaging with a standard gadolinium chelate is required for MRI. Scanning protocol should be per institutional standards, but should include at a minimum pre contrast T2 and a multi-phase dynamic pre- and post-contrast T1 weighted images in the axial plane. The inclusion of other imaging techniques/planes of imaging is per institutional/imaging center's standard.

For axial T2W and pre-post-gadolinium T1W series, image FOV should be per body habitus. Imaging matrix should be no less than 256 (frequency) x 128 (phase). For axial imaging, phase encoding should be anterior-posterior. Axial T2 weighted images can be performed per institutional standards, including fast/turbo spine echo (FSE/TSE), "fast-recovery" or "driven equilibrium" FSE techniques (e.g. FR-FSE), or "single shot" techniques ("SS-FSE" or "HASTE"). Fat saturation for T2W imaging is optional. Short tau inversion recovery (STIR) imaging cannot be substituted for FSE-based T2W imaging.

The multi-phase contrast enhanced T1W images can be performed as per local standards as long as the imaging plane, matrix, and slice thickness requirements are met. Multi-phase imaging will generally require the use of spoiled gradient echo techniques. Three-dimensional volumetric imaging is preferred, but multi-planar two-dimension imaging is acceptable. Fat saturation for T1W imaging is encouraged, but not required. All T1W images should be acquired using breath-held technique. Use of contrast agent and its dose should be according to institutional standards. For standard gadolinium chelates, a dose of 0.1 mmol/kg, injected at a rate of 2 cc/sec, is recommended. Saline flush (minimum 20cc) is required for MRI.

Pre-gadolinium T1W imaging is required for all MRI exams. Post gadolinium imaging should be performed using the exact imaging parameters as the pre-gadolinium study. The pre- and post-gadolinium images must be performed as a group. Post-gadolinium images must immediately follow the pre-gadolinium imaging to ensure standardization of imaging technique and gain settings. Pre-scan tuning should be performed once for the pre-gadolinium imaging and no further pre-scan tuning may be performed during the post-gadolinium imaging group.

Post-gadolinium imaging must include, at a minimum, a portal phase image (approximately 60-70 seconds after contrast injection). The additional arterial-phase imaging (approximately 20-30 seconds after contrast injection) and interstitial/delayed phase imaging (approximately 2-3 minutes after contrast injection) is strongly recommended.

1.2.2 Pelvic MRI

Pelvic imaging will be employed as part of total abdominal and pelvic imaging. Contrast-enhanced imaging is preferred. Pelvic MRI should include pre-gadolinium T1 and T2 weighted imaging in the axial plane. Specific sequences should be per institutional standards. Breath-held and free breathing imaging is acceptable. Contrast-enhanced imaging is encouraged and should be obtained approximately 1-2 minutes after contrast injection.

1.2.3 Chest MRI

Chest imaging will be performed if the patient has or is suspected to have involvement of disease in the chest at baseline. If documented chest disease involvement, all subsequent imaging will include chest scans. For assessment of chest disease, CT scanning is preferred. However, if MRI is utilized for evaluation of target liver lesions and required for assessment of non-target lesions, chest MRI may be performed.

Axial imaging must be performed. Imaging using T1W and T2W techniques is recommended. Specific imaging sequences are per institutional standards. Breath-held imaging is required. Contrast enhanced imaging is not required, but is recommended for T1W imaging. If chest MRI is performed in combination with abdominal imaging, chest imaging must precede abdominal imaging (i.e., non-contrast) or must be performed after abdominal imaging (i.e., delayed post-contrast).

2.0 CT/MRI Image Submission

All CT and MRI study exams must be submitted to ACRIN Image Management Center (IMC) for central review in support of the primary aim.

2.1 Electronic Transfer of CT/MRI Images

Digitally generated image files in DICOM v3.0 can be transmitted to ACRIN via FTP directly to the image archive. For further assistance in utilizing the electronic image submission option or for questions regarding image transfer, contact Cynthia Fenerty (cfenerty@phila.acr.org; 215-940-8863) or Adam Opanowski (aopanowski@phila.acr.org; 215-940-8890).

Removal of Confidential Patient Information: The header record on DICOM formatted image data, which usually contains the name of the patient, MUST be scrubbed before the image is transferred. This involves replacing the Patient Name tag with the SWOG case number and inserting the study number (ACRIN 6680 / SWOG S0518) into the other Patient ID tag. This can be performed using a customized software program or using a program available from ACRIN. Contact Cynthia Fenerty (cfenerty@phila.acr.org; 215-940-8863) or Adam Opanowski (aopanowski@phila.acr.org; 215-940-8890) for additional information.

2.2 CD Transfer

In the event that scrubbed image data cannot be electronically transferred, images may also be sent on media such as DVD or CD to the ACRIN IMC for transfer to the image archive; patient identifiers will be scrubbed appropriately at that time. Please contact Cynthia Fenerty (cfenerty@phila.acr.org; 215-940-8863) or Adam Opanowski (aopanowski@phila.acr.org; 215-940-8890) prior to submitting the first case on media to confirm compatibility.

2.3 Plain Film Images

It is highly preferred and recommended that the CT images are submitted in DICOM v3.0. However, in the circumstance where digital submission is not possible, contact the Image Management Center (IMC) for other submission options.

2.4 Missing and Delinquent Image Submission

ACRIN will provide the Southwest Oncology Group Statistical Center with a monthly report indicating the image sets received and those still due for submission. Sites experiencing difficulty with image submission due to technical factors should contact Cynthia Fenerty (cfenerty@phila.acr.org; 215-940-8863) or Adam Opanowski (aopanowski@phila.acr.org; 215-940-8890) at ACRIN for assistance in resolving these issues.

2.5 Image Quality Control

A review of the images submitted on the first two cases will be performed in order to ascertain the quality of image processing at the contributing institutions for adequate image quality. After the first two cases, 10% of all imaging studies submitted will be reviewed for quality control purposes. All images will be reviewed centrally by an expert radiologist(s) to support the imaging endpoint analysis. Sites will be notified of image quality issues and the Imaging staff will assist the local sites in correcting/resolving quality-related issues.

2.6 Imaging Transmittal Worksheet

a. Imaging exams must be submitted to the ACRIN Image Management Center after each imaging time-point/visit. A completed, signed Image Transmittal Worksheet must accompany all imaging exams submitted to ACRIN for each time-point. The Image Transmittal Worksheet is available on the S0518 abstract page on the SWOG website.

b. For exams submitted via the internet, complete this worksheet and e-mail to imagearchive@phila.acr.org or fax to 215-923-1737.

c. For exams submitted via media, complete this worksheet and include with the media shipment. Please affix a label to the jacket of the media to include: study name, site name, case no., date of exam(s), time-point, and type of imaging. Do not affix adhesive labels directly to the CD. Mail to:

ACRIN Image Management Center
American College of Radiology
1818 Market Street, Suite 1600
Philadelphia, PA 19103

For further information, questions or FTP info, contact Cynthia Fenerty (cfenerty@phila.acr.org; 215-940-8863) or Adam Opanowski (aopanowski@phila.acr.org; 215-940-8890).

3.0 Central Radiology Review

After registration, SWOG will provide ACRIN with the registration date and patient number, along with a blinded code indicating which reviewer will be assigned to each case. This ensures that each reader reviews a balanced number of cases from each study arm. An experienced radiologist will review each CT/MRI for assessment of progression of disease per RECIST criteria. The same reviewer will read all CT/MRI study exams of the study participant. Data from local reviews will not be provided to the central reviewers in order to keep the central reviewers blinded to the results of the local investigator-assessed PFS. Results of the central review will be collected on a CRF and entered into the database at ACRIN. Results of the ACRIN assessment will be transferred electronically to the SWOG Statistical Center. The result of this read will constitute the definitive radiographic assessment of progression.

If assessment of progression for a participant, based on central radiology review, is earlier than the local investigator/site assessment progression, the date of disease progression will be the date of the CT/MRI exam that documented the progression per the central radiology review. If central radiology review does not verify progression based on local radiographic assessment, ACRIN will continue to review any subsequent scans (if provided) to determine a later progression.

The actual progression will be determined at the SWOG Statistical Center, using a composite of the ACRIN assessment, in conjunction with possible data on progression from other sources or symptomatic deterioration (see Section 10.6). Results of the central review will NOT be communicated to the local site. Decisions regarding clinical management of the patient will be made by the treating physician based on local site assessments/reviews and other clinical considerations.

4.0 Radiology Review Procedures

Review of CT (or MRI) images will be performed using RECIST criteria.

4.1 Review of pre-treatment CT/MRI exam will be performed as follows:

The reader will review all anatomic areas (chest, abdomen, pelvis) imaged and available. The target lesions to be evaluated will be defined/determined by the review of the pre-treatment exam. A maximum of 10 target lesions will be defined with a maximum of 5 in a single organ. The 10 target lesions will be chosen with representation from all organs involved with the tumor. Additional significant non-target lesions and areas of non-measurable disease will be noted. A screen capture of each target lesion, annotated with a pointer and a lesion reference number assigned to the target lesion, will be generated and archived. This will be used on subsequent reads to ensure concordance of lesions on follow-up/post-treatment exams. Measurements will be made from the axial scan (generally the post contrast scan) that best demonstrates the lesion as distinct from background. All measurements will be made by electronic calipers. A screen capture of the actual measurement axis with calipers will be saved and archived with the exam permanently at ACRIN.

4.2 Review of post-treatment CT/MRI exam(s) will be performed as follows: The pre-treatment annotated exam and CRF will be reviewed to ensure lesion concordance. Readers will review all images for the current time point prior to making measurements. When performing lesion measurements on a scan from a given time point for a given target lesion, the previous measurement(s) of the specific target lesion will be reviewed to provide the reader with the previous axis and slice location for measurement. Measurements will be made from the axial post-contrast image that best demonstrates the lesion as distinct from background. Longest axis diameter will be recorded. Unless there is an obvious change in lesion shape, the reader will identify the slice on the current exam that best matches the lesion anatomy of the slice used for the prior measurement(s) and will choose an axis for diameter measurement that best approximates the axis used on the prior measurement(s). If there is an obvious change in lesion shape, a new axis that corresponds to the longest axis observed in the axial plane will be measured. All measurements will be made by electronic calipers. A screen capture of the actual measurement axis with calipers will be saved and archived with the exam permanently at ACRIN.

5.0 Central Review Quality Assurance

ACRIN will independently perform an internal audit on 30% of the baseline and first post-treatment exams. The information from the 30% sample that receive a central “re-read” will be documented for an assessment of interobserver discrepancies. The results of this review will not impact or be included in the primary aim analysis.

18.6 SPECT (Octreotide Scan) Study

Note: Due to the rarity of this disease (advanced/poor prognosis carcinoid) and the need to enroll patients from a large number of sites, ACRIN will not require sites to undergo the standard site qualification and approval process.

SPECT imaging is an optional, exploratory component of the trial. SPECT images may be performed as part of standard clinical management. If SPECT is performed, the scan should be acquired to a standard study protocol (detailed in Section 3.0). Images should be sent to ACRIN (per Section 6.0) where they will be analyzed and archived. Study sites are asked to submit:

- Baseline (pre-treatment) scan performed within 28 days prior to registration.
- Post-treatment scan performed at Week 9 (after Cycle 3, 0-3 days prior to Cycle 4)

1.0 Objectives

1.1 To assess and compare the prognostic and predictive value of the combination of In-111 pentetreotide somatostatin-receptor scintigraphy (SRS) and CT vs. CT in relation to progression-free survival (PFS)

1.2. To assess and compare the prognostic and predictive value of the combination of SRS and CT vs. CT in relation to overall survival (OS) and time to treatment failure (TTF).

2.0 Introduction: In-111 Pentetreotide Somatostatin-Receptor Scintigraphy (SRS)

Indium-111 pentetreotide is a [In-111 DTPA-D-Phe-] conjugate of octreotide, a somatostatin analog that binds to somatostatin receptors (predominantly somatostatin receptor subtypes sst2 and sst5). This octapeptide concentrates in neuroendocrine and some non-neuroendocrine tumors containing somatostatin receptors. The diagnostic radiolabeled peptide [^{111}In-DTPA]octreotide (OctreoScan, ^{111}In-pentetreotide) was approved by the Food and Drug Administration on June 2, 1994 for somatostatin-receptor scintigraphy (SRS) of patients with neuroendocrine tumors. In the intervening period, it has been proved that this technique permits the localization and staging of tumors that express the appropriate somatostatin receptors; the most important of these is receptor subtype 2 (sst2), because octreotide has the highest affinity for this subtype. The overall sensitivity of SRS in the detection of carcinoid tumors is approximately 86–95%. For extrahepatic lesions, sensitivity for lesions over 1 cm in diameter may exceed 90%; however, hepatic lesions may be isointense or only slightly hyperintense relative to normal hepatic parenchyma. Accordingly, single-photon emission computed tomography (SPECT) imaging of the liver is recommended even if the planar images appear normal (1). SPECT also is of value for detection and localization/characterization of extrahepatic tumor foci.

In-111 pentetreotide is cleared rapidly from the blood (one-third of the injected dose remains in the blood pool at 10 min, 1% at 20 hr postinjection). Excretion is almost entirely via the kidneys (50% of the injected dose is recovered in the urine by 6 hr, 85% within 24 hr). Hepatobiliary excretion is only about 2% of the administered dose.

In this study, we will review SRS with integrated or independently acquired CT studies. This is important if equivocal octreotide findings are explained by CT scan findings of an anatomic variation. Furthermore, the CT scan may help in deciding whether a particular area of increased In-111 pentetreotide uptake is localized to a mass or is associated with physiologic bowel or gallbladder activity.

3.0 SRS Imaging

- Baseline SRS must be obtained within 28 days prior to registration:

  [a] In patients who have received therapy prior to study entry, the baseline SRS study must be obtained at least 3 weeks after the last octreotide administration date.
  [b] In patients who are octreotide therapy-naïve, the baseline SRS study can be obtained at any time within 28 days prior to registration start date.

- Repeat SRS study at Week 9 (after Cycle 3 and 0-3 days prior to the start of Cycle 4).

3.1 General Procedures

- Patients should be well hydrated prior to and for at least one day after injection of In-111 pentetreotide.

- The use of laxatives should be considered, especially when the abdomen is the area of interest. A mild oral laxative (e.g., bisacodyl or lactulose) can be administered in the evening prior to injection and in the evening following injection. Laxatives should not be used in patients with active diarrhea.

- In-111 pentetreotide should not be injected into I.V. lines also being used for total parenteral nutrition.

- The administered activity of In-111 pentetreotide should be 6 mCi.

3.2 Image Acquisition

- Patients should void prior to imaging.

- Images are acquired at 24 ± 2 hrs post injection. Imaging at 48 ± 2 hrs may be needed when there is significant bowel activity at 24 hr that may be potentially obscuring lesions. Imaging at 4 hr is allowed, per institutional preference, but is not required.

- Planar images are acquired using a large field-of-view gamma camera fitted with a medium-energy collimator. Symmetrical 20% energy windows are centered over both photopeaks of In-111 (173 and 247 keV) and the data from both windows are used. Anterior and posterior whole-body images are acquired into 1024x512 word matrix using a dual-head camera with a speed of 3 cm/min including an area from the head to mid-femurs in a single pass. Separate planar spot images of the head, chest, abdomen, pelvis, and, the extremities may be acquired, as directed by the radiologist or nuclear physician, for 10–15 min per image, using a 256 x 256 word matrix.

- SPECT imaging of the appropriate regions should be performed at 24 hrs with a multidetector gamma camera (two or more detectors). For abdominal lesions, SPECT including the entirety of the liver must be acquired even if the planar images appear normal. Acquisition parameters for a multi-detector system will be: 3° angular sampling, 128 x 128 matrix, 360° rotation, 25-30 sec per stop.

- Local sites can use all set of images for interpretation. However, only the whole body images acquired at 24 and 48 hrs (if applicable) and SPECT data will be sent to the core laboratory for central reading.

3.3 Processing

In general, SPECT raw data are pre-filtered using an appropriate low-pass filter, per local preference and software manufacturer recommendations. The data are then reconstructed using an iterative reconstruction algorithm (preferred), or filtered back-projection, using a Wiener or Butterworth filter. Final reconstruction parameters should follow software manufacturer recommendations for SPECT with In-111 pentetreotide.

3.4 Quality Control

- Prior to the administration of In-111 pentetreotide, the labeling yield of the radiopharmaceutical should be tested according to the manufacturer's instructions. The product should not be used if radiochemical purity is less than 90%.

- The radiopharmaceutical should be used within 6 hr of preparation.

- In-111 pentetreotide should be inspected visually prior to administration. Preparations containing particulate matter or color should not be administered.

4.0 Image Analysis

For clinical purposes SRS studies will be interpreted locally. For study analyses, SRS studies will be interpreted centrally by readers blinded to patient outcome and to the clinical reading performed at the time of the actual study. Results of the central review and analysis will not be communicated to the local study sites.

4.1 Qualitative Analysis

4.1.1 SRS images should be evaluated in conjunction or fused with relevant anatomical images (e.g., CT, MRI).

4.1.2 Images are best viewed at the computer display with individualized physician-directed optimization of intensity and contrast. Three dimensional rendering of the SPECT data and its review in cinematic display will be performed and sent for central reading.

4.2 Evaluation Criteria for SPECT Data

4.2.1 Qualitative Evaluation of Target Lesions. The paired SRS studies (pre- and post-therapy) will be interpreted using 4 different response categories as follows:

(1) *Complete functional response (CFR)*: No abnormal tumor uptake on SRS (refer to section 3.2.1.2).
(2) *Partial functional response (PFR)*: Persistent abnormal tumor uptake on SRS , but with an appreciable reduction in intensity of tumor uptake or tumor volume by comparison with the baseline study. No disease progression at other sites.
(3) *Stable functional disease (SFD)*: No appreciable change in intensity of tumor uptake or tumor volume on SRS. No new sites of disease.
(4) *Progressive functional disease (PFD)*: Appreciable increase in tumor uptake or volume of target or non-target lesions. Interval development of new sites of disease.

4.2.2 Positive Reading for Disease: A positive lesion is defined as focal activity relatively higher than that of surrounding background tissue with no similar activity seen at the contralateral site, or increased activity in a location incompatible with normal anatomy or a normal variant. The background is considered as the highest activity in the evaluated cross section in a region that is considered normal, excluding pathological sites and those sites with high physiologic or artifactual uptake.

4.2.3 Negative Reading for Disease: A negative study is defined as having no pathological uptake at any site, including all sites of previously increased pathological uptake.

Pre-therapy and post-therapy evaluation of disease will be performed on a site-by-site analysis for the involved disease sites. The qualitative results obtained in 4 different categories, will be dichotomized and correlated with the patients response status in relation to PFS, OS, TTF.

4.3 Quantitative Analysis: Only SPECT images will be used for quantitative analysis.

In patients with multiple tumor sites, the 5 sites with the highest uptake will be designated as the target sites. For these lesions, the tumor-to-background (T/B) ratio will be determined at baseline and after 3 cycles of therapy.

Step 1. At baseline a region of interest will be drawn over the tumor on an axial SPECT slice that visually shows the most prominent uptake. Average counts using a 2x2 pixel size region over the most intense part of the lesion will be obtained. A similar region of interest with a 3x3 pixel size will be obtained in the thigh to be used as the background. The T/B ratio will be calculated.

Step 2. After 3 cycles of therapy, average counts using a 2x2 pixel size region over the most intense part of the lesion will be obtained within the tumor on an axial SPECT slice that visually shows the most prominent uptake (if any uptake). A similar region of interest with a 3x3 pixel size will be obtained in the thigh to be used as the background. The T/B ratio will be calculated.

Step 3. Absolute percent decrease in T/B ratios between baseline and after therapy will be obtained. The quantitative data will be used as continuous measurements in the analysis of prognostic and predictive performance.

5.0 Statistical Considerations

Patients enrolled in this study will undergo SRS, including SPECT, and CT scanning at baseline and after the 3rd cycle of therapy. Qualitative and quantitative central interpretations of the imaging scans will be performed as described above. The prognostic and predictive values of SPECT and CT will be assessed using the available qualitative data and, in the case of SPECT, the quantitative assessments as well. All analyses of these data will be exploratory in nature.

5.1 To assess and compare the prognostic and predictive value of the combination of In-111 pentetreotide somatostatin-receptor scintigraphy (SRS) and CT vs CT in relation to progression-free survival (PFS)

5.2 To assess and compare the prognostic and predictive value of the combination of SRS and CT vs CT in relation to overall survival (OS) and time to treatment failure (TTF).

5.3 In the analysis of the performance of qualitative assessments of response to therapy by SRS and CT we will use Cox regression models in which the dependent variable will be PFS (Aim 1.1), OS or TTF (Aim 1.2). Appropriately constructed indicator variables for the qualitative response assessments will be entered in each model and measures of predictive performance of the model (notably the C statistic [Ref 2]) will be estimated. For each modality (SPECT and CT) separate models will be estimated, with and without indicator variables for therapy. The models without therapy indicators will assess the prognostic value of the modality. The models with therapy indicators will be used to assess the presence of interactions with type of therapy and will assess the predictive value of the modality. The predictive strength of the Cox regression models will be compared on the basis of their C statistic.

5.4 The prognostic and predictive value of the quantitative data from SPECT (absolute percent decrease in T/B ratios between baseline and after therapy) will also be assessed. Two approaches will be used to provide complementary perspectives on the performance of SPECT for each task: (a) Cox regression modeling with the SPECT measure as independent variable and PFS, OS or TTF as the dependent variable. As in the case of the qualitative analysis, models with and without indicator variables for treatment group will be considered. The predictive value of SPECT will be assessed on the basis of the presence and magnitude of an interaction between SPECT measurement and treatment. (b) Time dependent ROC analysis will be used in which the test result will be the SPECT measurement and the time dependent reference standard will be provided by the variables indicating PFS, OS or TTF (Ref 3). In addition to assessing the overall performance of the quantitative SPECT information, the analysis will examine alternative threshold values for declaring a “response” by quantitative SPECT criteria.

6.0 Image Submission

Study sites are asked to submit SPECT images for all study participants whom receive a SPECT (SRS, Octreotide Scan) as part of her/his clinical management. Three dimensional rendering of the SPECT data (as described in Section 4.0) and its review in cinematic display will be performed and sent for central reading.

6.1 Electronic Transfer of SPECT Images

Digitally generated image files in DICOM v3.0 can be transmitted to the ACRIN via FTP directly to the image archive. For further assistance in utilizing the electronic image submission option or for questions regarding image transfer, contact Cynthia Fenerty (cfenerty@phila.acr.org; 215-940-8863) or Adam Opanowski (aopanowski@phila.acr.org; 215-940-8890).

Removal of Confidential Patient Information: The header record on DICOM formatted image data, which usually contains the name of the patient, MUST be scrubbed before the image is transferred. This involves replacing the Patient Name tag with the ACRIN and SWOG case number and inserting the study number (ACRIN 6680 / SWOG **S0518**) into the other Patient ID tag. This can be performed using a customized software program or using a program available from ACRIN. Contact Cynthia Fenerty (cfenerty@phila.acr.org; 215-940-8863) or Adam Opanowski (aopanowski@phila.acr.org; 215-940-8890) for additional information.

6.2 CD Transfer

In the event that scrubbed image data cannot be electronically transferred, images may also be sent on media such as DVD or CD to the ACRIN IMC for transfer to the image archive; patient identifiers will be scrubbed appropriately at that time. Please contact Cynthia Fenerty (cfenerty@phila.acr.org; 215-940-8863) or Adam Opanowski (aopanowski@phila.acr.org; 215-940-8890) prior submitting the first case on media to confirm compatibility.

6.3 Plain Film Images

Plain film images of the SPECT scan are not acceptable for this study. It is highly preferred that images are submitted in DICOM 3.0, however, in circumstance where this is not possible contact Cynthia Fenerty (cfenerty@phila.acr.org; 215-940-8863) or Adam Opanowski (aopanowski@phila.acr.org; 215-940-8890).

6.4 Missing and Delinquent Image Submission

ACRIN will provide the Southwest Oncology Group Statistical Center with a monthly report indicating the image sets received and those still due for submission. Sites experiencing difficulty with image submission due to technical factors should contact Cynthia Fenerty (cfenerty@phila.acr.org; 215-940-8863) or Adam Opanowski (aopanowski@phila.acr.org; 215-940-8890) at ACRIN for assistance in resolving these issues.

6.5 Image Quality Control

A review of the images submitted on the first two cases will be performed in order to ascertain the quality of image processing at the contributing institutions for adequate image quality. After the first two cases, 10% of all imaging studies submitted will be reviewed for quality control purposes. All images will be reviewed centrally by an expert radiologist(s) to support the imaging endpoint analysis. Sites will be notified of image quality issues and the Imaging staff will assist the local sites in correcting/resolving quality-related issues.

6.6 Imaging Transmittal Worksheet

a. Imaging exams must be submitted to the ACRIN Image Management Center after each imaging time-point/visit. A completed, signed Image Transmittal Worksheet must accompany all imaging exams submitted to ACRIN for each time-point. The Image Transmittal Worksheet is available on the **S0518** abstract page on the SWOG website.

b. For exams submitted via the internet, complete this worksheet and e-mail to imagearchive@phila.acr.org or fax to 215-923-1737.

c. For exams submitted via media, complete this worksheet and include with the media shipment. Please affix a label to the jacket of the media to include: study name, site name, case no., date of exam(s), time-point, and type of imaging. Do not affix adhesive labels directly to the CD. Mail to:

ACRIN Image Management Center
American College of Radiology
1818 Market Street, Suite 1600
Philadelphia, PA 19103

For further information, questions or FTP info, contact Cynthia Fenerty (cfenerty@phila.acr.org; 215-940-8863) or Adam Opanowski (aopanowski@phila.acr.org; 215-940-8890).

Reference

1. de Herder WW, Kwekkeboom DJ, Valkema R, et al. Neuroendocrine tumors and somatostatin: imaging techniques. J Endocrinol Invest. 2005;28(11 Suppl):132-6.

2. Harrell F, Lee K. and Mark D. Multivariate prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Statistics in Medicine, 1996, 15: 361-387

3. Heagerty, P Lumley, T and Pepe, M. Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics 2000; 56: 337-344.

18.7 CTSU Participation Procedures

REGISTRATION/RANDOMIZATION

Prior to 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, 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 registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site at http://members.ctsu.org

All forms and documents associated with this study can be downloaded from the **S0518** Web page on the CTSU registered member Web site (https://members.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

Requirements for S0518 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Prestudy requirements for patient enrollment on S0518

- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms
- All baseline laboratory tests and prestudy evaluations performed.

CTSU Procedures for Patient Enrollment

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.
2. Complete the following forms:
   - CTSU Patient Enrollment Transmittal Form
   - Eligibility Criteria Checklist (Section 5.0 of the protocol)
   - SWOG Registration Form (Complete all sections of form except for SWOG-specific data fields)
3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays). The CTSU 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 follow-up with the site to resolve any discrepancies.

4. Once investigator eligibility is confirmed and enrollment documents deemed complete, the CTSU registrar will contact the Southwest Oncology Group, to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will convey this information to the enrolling site and follow up with a confirmation via e-mail or fax.

   Patients must be registered prior to initiation of treatment (no more than three working days prior to planned start of treatment).

DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) associated with this study must be downloaded from the S0518 Web page located on the CTSU registered member Web site (https://members.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the SWOG Data Operations Center. The preferred method of sending data is via fax at 800/892-4007, (large volumes of data may be sent via post, see contacts table for mailing address). Do NOT include a cover sheet for faxed data.

3. The SWOG Data Operations Center will send query notices and delinquency reports directly to the site for reconciliation. Please fax query responses and delinquent data to the SWOG Data Operations Center and do not copy the CTSU Data Operations. When faxing data, include the query sheet that was originally sent from SWOG.

4. Each site should have a designated CTSU Administrator and Data Administrator and **must keep their CTEP AMS account contact information current.** This will ensure timely communication between the clinical site and the SWOG data center.

SPECIAL MATERIALS OR SUBSTUDIES

All specimens submitted for this study must be entered and tracked using the SWOG on-line Specimen Tracking System, as specified in protocol Section 15.0.

You can also access the Tracking System from the CTSU Member Web Site. Go to the **S0518** protocol page and click on the link provided under the Case Report Forms header.

Specimen collection for correlatives (Protocol Section 15.0)

- The submission of tissue is mandatory for all patients on this study. Tissue will be used for pathology review and for the VEGF testing described in Appendix 18.2. Instructions on tissue submission are outlined in protocol Section 15.2.a.
- Institutions are required to seek patient consent for submission of blood. Blood samples will be used for the testing of angiogenic markers described in Appendix 18.2. Blood collection and shipping instructions are outlined in protocol Section 15.2.b.

Radiology Review (Protocol Section 15.0):

- CT / MRI Imaging
  Institutions are required to submit all CT/MRI scans for central radiology review. Instructions on radiology review can be found in protocol Section 15.1 and Appendix 18.5.

- SPECT Imaging
  Patients who undergo SPECT imaging as part of their standard clinical care are asked to submit 2 SPECT scans, one at baseline and then again after the third treatment cycle. This is an optional component of the trial and requires additional patient consent and second registration. See protocol Section 15.1 and Appendix 18.6 for further details.

SERIOUS ADVERSE EVENT (AE) REPORTING (SECTION 16.0)

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.

2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Reporting System (CTEP-AERS) from either the Adverse Events tab of the CTSU member homepage (https://members.ctsu.org) or by selecting Adverse Event Reporting Forms from the document center drop down list on the **S0518** Web page.

3. Do not send adverse event reports to the CTSU.

4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu of CTEP-AERS. Submit the completed form and supporting documentation as outlined in the protocol.

DRUG PROCUREMENTS (SECTION 3.0)

CTSU investigators should refer to Section 3.0 for detailed instructions on drug procurement, formulation, storage and accountability, administration, and potential toxicities.

Investigational agents: Bevacizumab

Completed Clinical Drug Requests (NIH-986) for PMB-distributed agents should be submitted to the PMB by FAX (301)-480-4612 or mailed directly to the Pharmaceutical Management Branch. The PMB will ship drug only to the shipping address specified by the CTSU investigator on their Supplemental Investigator Data Form.

Commercial agents: Interferon Alpha-2b, Octreotide acetate for injectable suspension
Interferon Alpha-2b and Octreotide acetate for injectable suspension are commercially available and should be purchased by a third party.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. (e.g., NSABP members may only request credit for protocols pertaining to breast or colorectal cancers). Registrations to protocols for other disease sites may still take place through CTSU without receiving credit for your NSABP activities. Per capita reimbursement will be issued directly from CTSU.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data Update System (CDUS) Monitoring

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. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.