SUMMARY OF CHANGES - PROTOCOL

Protocol Amendment # 6: This protocol is being submitted to update the Comprehensive Adverse Events and Potential Risks list (CAEPR) and the study design in the protocol

NCI Protocol #: 9604
Local Protocol #: 2013-0954

NCI Version Date: January 11, 2018
Protocol Date: January 11, 2018

#	Section	Page	Change
1.	Protocol Title Page	1	**OLD TEXT:** **Protocol Type / Version # / Version Date:** Version 4 / January 15, 2016 Version 5 / Version Date: November 9, 2017 **NEW TEXT:** **Protocol Type / Version # / Version Date:** Version 5 / Version Date: September 29, 2016 **Version 6 / Version Date: January 11, 2018** **RATIONALE:** Updated Version Date
2.	7.ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS	35	**OLD TEXT:** **7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs) for Ziv-aflibercept (VEGF-Trap, AVE 0005, NSC 724770)** The Comprehensive Adverse Events 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 811 patients.* Below is the CAEPR for Ziv-aflibercept (VEGF-Trap, AVE 0005). **NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required. **Version 2.6, November 24, 2015[1]**

Adverse Events with Possible Relationship to Ziv-aflibercept (VEGF-Trap, AVE 0005) (CTCAE 4.0 Term) [n= 811]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			*Anemia (Gr 2)*
		Febrile neutropenia	
		Hemolytic uremic syndrome	
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Chest pain - cardiac	
		Myocardial infarction	
		Restrictive cardiomyopathy	
		Cardiac disorders - Other (intracardiac thrombus)	
GASTROINTESTINAL DISORDERS			
Abdominal pain			*Abdominal pain (Gr 2)*
	Anal mucositis		
	Constipation		*Constipation (Gr 2)*
	Diarrhea		*Diarrhea (Gr 2)*
		Gastrointestinal fistula*	
		Gastrointestinal perforation*	

#	Section	Page	Change

	Mucositis oral		
Nausea			*Nausea (Gr 2)*
	Vomiting		*Vomiting (Gr 2)*
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		*Edema limbs (Gr 2)*
Fatigue			*Fatigue (Gr 3)*
	Fever		*Fever (Gr 2)*
	Pain		
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		
INFECTIONS AND INFESTATIONS			
	Infection*		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Wound complication		
	Wound dehiscence		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		
Lymphocyte count decreased			*Lymphocyte count decreased (Gr 4)*
	Neutrophil count decreased		*Neutrophil count decreased (Gr 4)*
	Platelet count decreased		*Platelet count decreased (Gr 4)*
	Weight loss		
	White blood cell decreased		*White blood cell decreased (Gr 2)*
METABOLISM AND NUTRITION DISORDERS			
Anorexia			*Anorexia (Gr 2)*
	Dehydration		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		*Arthralgia (Gr 2)*
	Back pain		
	Myalgia		*Myalgia (Gr 2)*
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Headache			*Headache (Gr 3)*
		Ischemia cerebrovascular	*Ischemia cerebrovascular (Gr 2)*
		Reversible posterior leukoencephalopathy syndrome	
		Transient ischemic attack	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Proteinuria		*Proteinuria (Gr 3)*
		Renal disorders - Other (nephrotic syndrome)	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
	Genitourinary system fistula[a]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		*Cough (Gr 2)*

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Adverse Events with Possible Relationship to Ziv-aflibercept (VEGF-Trap, AVE 0005) (CTCAE 4.0 Term) [n= 811]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dyspnea		*Dyspnea (Gr 3)*
	Pharyngolaryngeal pain		
Voice alteration			*Voice alteration (Gr 2)*
	Respiratory, thoracic, and mediastinal disorders - Other (rhinorrhea)		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Palmar-plantar erythrodysesthesia syndrome		
	Rash maculo-papular		
	Skin hyperpigmentation		
VASCULAR DISORDERS			
Hypertension			*Hypertension (Gr 3)*
	Thromboembolic event		*Thromboembolic event (Gr 3)*
	Vascular disorders - Other (hemorrhage)[6]		*Vascular disorders - Other (hemorrhage)[6] (Gr 2)*

[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]Gastrointestinal fistulas may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal perforation imay include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[4]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[5]Genitourinary fistulas may include: female genital tract fistula, uterine fistula, and vaginal fistula.

[6]The majority of hemorrhage events were mild. Major events, defined as symptomatic bleeding in a critical area or organ (e.g., eye, GI hemorrhage, GU hemorrhage, respiratory hemorrhage), and nervous system [including fatal intracranial hemorrhage and cerebrovascular accident] have been reported.

Adverse events reported on Ziv-aflibercept (VEGF-Trap, AVE 0005) trials but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ziv-aflibercept (VEGF-Trap, AVE 0005) caused the event.

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (hemoglobin increased); Hemolysis
CARDIAC DISORDERS - Acute coronary syndrome; Cardiac disorders - Other (left ventricular diastolic dysfunction); Heart failure; Left ventricular systolic dysfunction; Pericarditis; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus; Vertigo
ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Extraocular muscle paresis; Eye disorders - Other (blindness transient); Eye

#	Section	Page	Change
			disorders - Other (diplopia); Vitreous hemorrhage **GASTROINTESTINAL DISORDERS** - Abdominal distension; Colitis; Dental caries; Dry mouth; Dyspepsia; Dysphagia; Esophageal pain; Flatulence; Gastritis; Gastrointestinal disorders - Other (early satiety); Gastrointestinal disorders - Other (enteric fistula); Gastrointestinal disorders - Other (eructation); Gastrointestinal disorders - Other (gastrointestinal necrosis); Gastrointestinal disorders - Other (hiatal hernia);Gastrointestinal disorders - Other (intestinal ischemia); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal disorders - Other (peritonitis); Gingival pain; Hemorrhoids; Ileus; Oral pain; Rectal mucositis; Rectal ulcer; Small intestinal mucositis; Small intestinal obstruction **GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Edema face; Edema trunk; Facial pain; Infusion related reaction; Injection site reaction; Non-cardiac chest pain **HEPATOBILIARY DISORDERS** - Cholecystitis **INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Biliary anastomotic leak; Gastric anastomotic leak; Vascular access complication **INVESTIGATIONS** - Activated partial thromboplastin time prolonged; Blood bilirubin increased; Creatinine increased; Ejection fraction decreased; GGT increased; Investigations - Other (elevated LDH) **METABOLISM AND NUTRITION DISORDERS** - Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia **MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Arthritis; Avascular necrosis; Chest wall pain; Generalized muscle weakness; Head soft tissue necrosis; Joint range of motion decreased; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Musculoskeletal and connective tissue disorder - Other (musculoskeletal stiffness); Musculoskeletal and connective tissue disorder - Other (rotator cuff tear); Myositis; Neck pain; Osteonecrosis of jaw; Pain in extremity; Pelvic soft tissue necrosis **NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage) **NERVOUS SYSTEM DISORDERS** - Amnesia; Ataxia; Cognitive disturbance; Dysgeusia; Encephalopathy; Extrapyramidal disorder; Leukoencephalopathy; Memory impairment; Paresthesia; Peripheral sensory neuropathy; Seizure; Syncope; Vagus nerve disorder **PSYCHIATRIC DISORDERS** - Anxiety; Confusion; Depression; Insomnia; Psychiatric disorders - Other (mental status change); Psychosis **REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Irregular menstruation **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Hypoxia; Laryngeal mucositis; Nasal congestion; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary fibrosis; Respiratory, thoracic and mediastinal disorders - Other (nasal dryness); Respiratory, thoracic and mediastinal disorders - Other (tracheal fistula); Respiratory, thoracic and mediastinal disorders - Other (septal perforation); Tracheal mucositis **SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Dry skin; Hyperhidrosis; Nail loss; Rash acneiform; Skin and subcutaneous tissue disorders - Other (hyperemia); Skin ulceration **VASCULAR DISORDERS** - Hematoma; Hypotension; Peripheral ischemia; Phlebitis **Note**: Ziv-aflibercept (VEGF-Trap, AVE 0005) 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. **NEW TEXT:**

#	Section	Page	Change

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Ziv-aflibercept (VEGF-Trap, AVE 0005, NSC 724770)

The Comprehensive Adverse Events 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 941 patients.* Below is the CAEPR for Ziv-aflibercept (VEGF-Trap, AVE 0005).

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Version 2.7, October 2, 2017[1]

Adverse Events with Possible Relationship to Ziv-aflibercept (VEGF-Trap, AVE 0005) (CTCAE 4.0 Term) [n= 941]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
		Febrile neutropenia	
		Hemolytic uremic syndrome	
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Cardiac disorders - Other (intracardiac thrombus)	
		Chest pain - cardiac	
		Myocardial infarction	
		Restrictive cardiomyopathy	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***

#	Section	Page	Change

		Gastrointestinal fistula[2]	
		Gastrointestinal perforation[3]	
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Pain		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Wound complication		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		
	Creatinine increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
Headache			***Headache (Gr 3)***
		Ischemia cerebrovascular	***Ischemia cerebrovascular (Gr 2)***
		Reversible posterior leukoencephalopathy syndrome	
		Transient ischemic attack	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
Proteinuria			***Proteinuria (Gr 3)***
		Renal and urinary disorders - Other (nephrotic syndrome)	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
	Genitourinary system fistula[4]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***

#	Section	Page	Change

	Dyspnea		***Dyspnea (Gr 3)***
	Respiratory, thoracic and mediastinal disorders - Other (rhinorrhea)		
Voice alteration			***Voice alteration (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Palmar-plantar erythrodysesthesia syndrome		
	Skin hyperpigmentation		
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3.	Study Design/Sample Size Stopping Rule 1	60	**OLD TEXT:** Stopping rule 1: The first early stopping rule applies to all patients by applying the Simon's optimal two-stage design. In the first stage, we will enroll 21 evaluable patients. If 0 or 1 of the first 21 patients achieve RECIST response (PR or CR), the study will terminate. If at least 2 of the first 21 evaluable patients achieve RESCIST response (PR or CR), an additional 20 patients will be enrolled. If at the end of

#	Section	Page	Change
			the second stage, at least 5 out of 41 patients achieve RECIST response, the treatment will be considered acceptable for further testing. This design has a ~~3.9~~% chance of accepting the treatment for further testing if the true response rate is ≤ 5% (type 1 error = 0.046), and ~~90~~% power (type 2 error = 0.1) of accepting the treatment for further testing if the true response rate is at least 20%. The maximal accrual will be 41 evaluable patients. The probability of early termination is 72% under the null hypothesis. **NEW TEXT:** The first early stopping rule applies to all patients by applying the Simon's optimal two-stage design. In the first stage, we will enroll 21 evaluable patients. If 0 or 1 of the first 21 patients achieve RECIST response (PR or CR), the study will terminate. If at least 2 of the first 21 evaluable patients achieve RESCIST response (PR or CR), an additional 20 patients will be enrolled. If at the end of the second stage, at least 5 out of 41 patients achieve RECIST response, the treatment will be considered acceptable for further testing. This design has a **4.6**% chance of accepting the treatment for further testing if the true response rate is ≤ 5% (type 1 error = 0.046), and **85**% power (type 2 error = 0.1**5**) of accepting the treatment for further testing if the true response rate is at least 20%. The maximal accrual will be 41 evaluable patients. The probability of early termination is 72% under the null hypothesis. RATIONALE: Given the inclusion of more heavily pretreated patients, the response rate under the null hypothesis was reduced, and the response rate under the alternative hypothesis was simultaneously adjusted (from 0.21 to 0.2) for simplicity. Type I and type II error rates were simultaneously adjusted (from 0.084 to 0.05 and from 0.1 to 0.15, respectively) based on our own recent work regarding the predictive value of phase II studies, demonstrating that smaller type I errors with compensatory increases in type II error rates result in phase II designs more likely to predict for eventual drug efficacy and approval. These changes resulted in changes to the total number of patients anticipated to be accrued, resulting in new calculations for the imaging parameter power calculations.

NCI Protocol #: 9604

Local Protocol #: 2013-0954

TITLE: Perfusion CT as predictive biomarker in a phase II study of ziv-aflibercept in patients with advanced pancreatic neuroendocrine tumors

Coordinating Center: University of Texas MD Anderson Cancer Center

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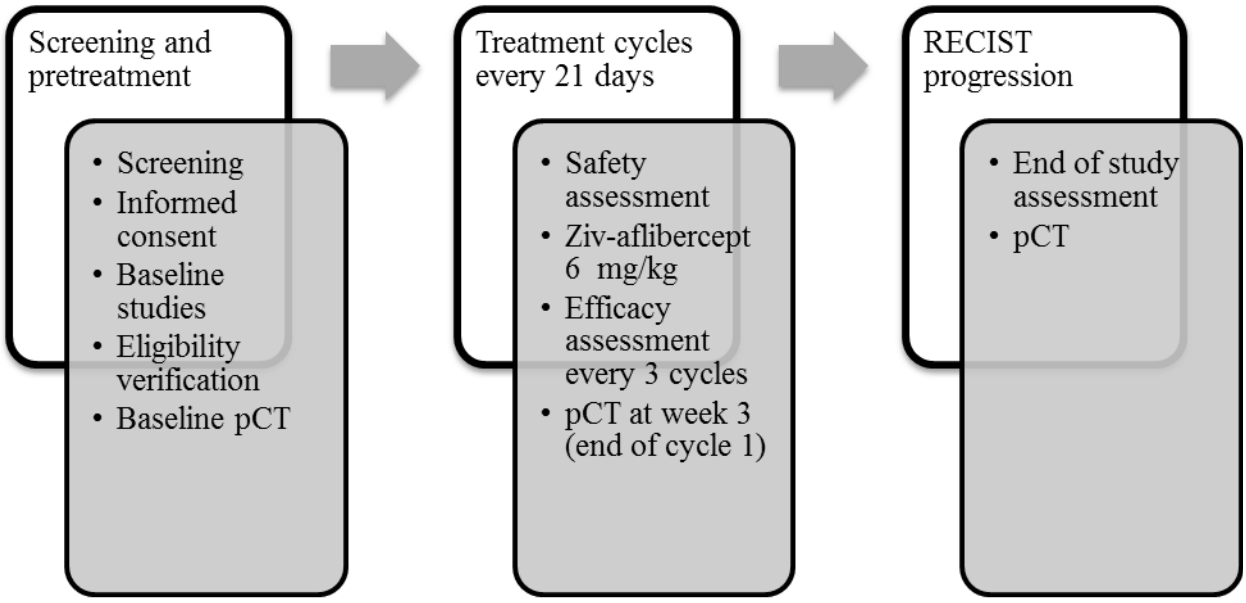
NCI-Supplied Agent(s): Ziv-aflibercept (NSC 724770)
Other Agent(s): Not applicable

IND #: 100137

IND Sponsor: NCI Division of Cancer Treatment and Diagnosis (DCTD)

Protocol Type / Version # / Version Date:
Original / Version 4 / Version Date: January 15, 2016
Version 5 / Version Date: September 29, 2016
Version 6/ Version Date: January 11, 2018

SCHEMA



Perfusion CT (pCT) will be conducted as advanced imaging in this study. pCT will be conducted at baseline, week 3 (end of cycle 1), and time of progression.

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 Estimate the objective response rate (RR) of ziv-aflibercept among patients with advanced pancreatic neuroendocrine tumors (NET)s according to RECIST 1.1

1.1.2 Test the following hypotheses: that baseline perfusion CT parameters can predict which patients with advanced pNETs will respond to treatment with ziv-aflibercept. Specifically:

a. Pancreatic NETs with high baseline blood volume (BV > 5.25 ml/100gram) measured by pCT will have a higher response rate to therapy with ziv-aflibercept than those with low baseline BV (BV ≤ 5.25ml/100gram).
b. Pancreatic NETs with high baseline permeability surface (PS > 25 ml/minute/100gram) measured by pCT will have a higher response rate to therapy with ziv-aflibercept than those with low baseline PS (PS ≤ 25 ml/minute/100gram).

1.2 Secondary Objectives

1.2.1 Estimate progression free survival (PFS) duration among patients treated with ziv-aflibercept

1.2.2 Evaluate the relationship between response rate and baseline BV and between response rate and baseline PS

1.3 Exploratory Objectives

1.3.1 Determine whether post-treatment changes in BV expressed as relative change from baseline correlate with response to ziv-aflibercept
1.3.2 Determine whether post-treatment tumor blood flow (BF) (absolute measurement) correlates with response to ziv-aflibercept
1.3.3 Determine whether post-treatment changes in BF and, BV, expressed as relative change from baseline, correlate with relative change in sum of tumor diameters (RECIST 1.1measurements)
1.3.4 Determine the effect of ziv-aflibercept therapy on post-treatment blood flow (BF), BV, mean transit time (MTT), and PS at 4 weeks after treatment
1.3.5 Evaluate the changes in tumor perfusion parameters at time of progression

2. BACKGROUND

2.1 Pancreatic NETs

Pancreatic NETs are low- to intermediate-grade neoplasms that are thought to arise from the pancreatic islets. Also known as pancreatic endocrine tumors and, islet cell tumors, or pancreatic carcinoid, PNETs account for a minority of pancreatic neoplasms and can be either functional or

nonfunctional. The functional status of pancreatic NETs is generally influenced by several factors, including disease bulk, stage, secretory status, and whether the peptide secreted is intact and causes distinct clinical symptoms. Pancreatic NETs are generally considered functional if they are associated with a hormonal syndrome. Those pancreatic NETs not causing a clinical hormonal syndrome are considered nonfunctional. It is also recognized that the functional status of these tumors may change over time or with treatment. Moreover, some of these tumors can produce multiple hormones simultaneously, although symptoms related to one of these hormones often will dominate.

Pancreatic NETs are reputed to be relatively rare neoplasms, but their exact incidence and prevalence are somewhat elusive. This is in part because most registries, including the Surveillance, Epidemiology, and End Results (SEER) Program, only include neoplasms that are deemed malignant. For most epithelial malignancies, invasion of the basement membrane defines malignant behavior, but for pancreatic NETs, the definition of malignant behavior is more complex. In absence of malignant behavior such as direct invasion of adjacent organs or metastases to regional lymph nodes or distant sites, size is typically used to classify pancreatic NETs as benign or malignant. We recently undertook comprehensive population-based analyses of NETs from SEER registries between 1973 and 2004. The annual age-adjusted incidence of NETs arising from the pancreas in the periods covered by the SEER 17 (2000-2004) was 0.32 per 100,000 population, respectively.(1) Malignant well-differentiated pancreatic NETs accounts for approximately 1% of pancreatic cancers by incidence and 10% of pancreatic cancers by prevalence. (2)

The incidence of smaller pancreatic NETs in the general population, however, is likely to be much higher. For example, surgical series suggest that most insulinomas are small and localized, yet in the SEER registries, 61% of insulinomas had distant metastases at diagnosis,(2) a finding that suggests that most of the small insulinomas are not being included in those statistics. Furthermore, in an analysis of 11,472 autopsies performed at a Hong Kong hospital, pancreatic NETs were found in 0.1% of all cases.(3) This suggest that the prevalence of small asymptomatic islet cell tumors, many of which are never diagnosed, may be 100 fold more common than the data suggested by SEER registries.

Pancreatic NETs are usually more indolent than the more common forms of pancreatic cancer are. Management of pancreatic NETs generally can be categorized into management of the problems caused by secreted hormone(s) and oncologic issues related to tumor growth and management of metastasis. While somatostatin analogues are quite active and standard of care for hormonal syndromes from pancreatic NETs, the oncologic management of advanced pancreatic NETs remains an area of unmet need.

Streptozocin-based chemotherapy was approved by the Food and Drug Administration for the treatment of pancreatic NET nearly three decades ago. Analyses of 2 large case-series using Response Evaluation Criteria of Solid Tumors (RECIST) criteria have reported objective tumor response rates of 38 and 39% (4, 5). However, the exact role of streptozocin-based chemotherapy is still debated due to potentially serious adverse events and conflicting data about efficacy.

Genetic cancer syndromes (TSC-2, NF-1, and vHL), somatic mutations identified using an

exome sequencing approach, and expression profiling have consistently implicated a dysfunction of the mammalian target of rapamycin (mTOR) pathway as a critical event in pancreatic NETs (6-8). Everolimus, an oral inhibitor of mTOR, was studied in a multi-national double blind placebo controlled phase III study (9). The study demonstrated that everolimus significantly prolonged median progression free survival (PFS) from 4.6 to 11 months compared to placebo (Hazard Ratio [HR] = 0.35, 95% Confidence Interval [CI], 0.27 - 0.45; P<0.0001). Everolimus also significantly reduced insulin, glucagon and gastrin secretions among patients with functional pancreatic NETs (10, 11).

NETs are vascular tumors. Hence, there is also strong rationale to study anti-angiogenic agents in NETs. Sunitinib, an inhibitor of vascular endothelial growth factor (VGEF) and platelet-derived growth factor (PDGF) receptors, was also studied in a double-blinded placebo-controlled phase III study (12). Treatment with sunitinib 37.5 mg daily was associated with an improvement in median PFS from 5.5 to 11.4 months (HR = 0.42, 95% CI, 0.26 - 0.66) (12). Although the study failed to achieve statistical significance due to unplanned interim analyses and early termination, its results are supported by other studies of VEGF inhibitors in pancreatic NET (13-15). Additionally, evidence from renal cell carcinoma suggests that multiple VEGF inhibiting agents can be used in series with continued efficacy. In a study of renal cell carcinoma patients who had previously received sunitinib, pazopanib resulted in objective responses in 6/31 (19%) patients, including 3/18 (17%) of the patients who discontinued sunitinib due to disease progression(16).

Results from these two randomized phase III studies led to the approval of everolimus and sunitinib for the treatment of pancreatic NET and changed the treatment paradigm. However, it should be noted that the objective response rates for everolimus and sunitinib are low and predictive markers of benefit remains undefined.

2.2 CTEP IND Agent: Ziv-aflibercept

Background and pharmacological mode of action

Ziv-aflibercept is also referred to as "AVE0005," "AVE0005 (VEGF Trap)," "VEGF Trap," "V-Trap," and "VGFT" in various clinical study protocols and other documents. However, it will be referred to by its international non-proprietary name (INN), ziv-aflibercept, throughout this protocol (Investigator's Brochure, 2011).

Ziv-aflibercept is a recombinant fusion protein consisting of human vascular endothelial growth factor (VEGF) receptor extracellular domains fused to the Fc portion of human immunoglobulin G1 (IgG1). Ziv-aflibercept contains portions of the extracellular domains of 2 different vascular endothelial growth factor receptors (VEGFRs): VEGFR1 (also known as Flt-1) and VEGFR2 (also known as KDR or Flk-1). Ziv-aflibercept binds VEGF in the picomolar (pmol/L) range, and also binds placental growth factor (PlGF), although with lower affinity. The affinity constants (KD) for binding to 2 human isoforms of VEGF, VEGF165 and VEGF121, are 0.50 pmol/L and 0.36 pmol/L, respectively. The KD for human PlGF2 is 39 pmol/L. The binding of ziv-aflibercept to its ligands in vivo is expected to block tumor angiogenesis and vascular permeability (Investigator's Brochure, 2011).

Ziv-aflibercept drug product is formulated as a sterile liquid for intravenous (IV) administration. Ziv-aflibercept has been found to be active with a broad pharmacological index against early and advanced stage disease in a variety of preclinical solid tumor models including sarcomas, and ovarian, prostate, mammary, colon, and gastric carcinomas when used as a single agent or in combination with cytotoxic agents. In mouse models of ascites formation with ovarian and renal cell carcinoma, ziv-aflibercept inhibited ascites formation and reduced tumor burden (Investigator's Brochure, 2011).

Two analytes were assayed in animal models specifically by enzyme linked immunosorbent assay (ELISA) methods: free ziv-aflibercept (compound not complexed to VEGF), and bound ziv-aflibercept (complexed ziv-aflibercept: VEGF [ratio 1/1]) (Investigator's Brochure, 2011).

Following IV administration in all animal species evaluated, free ziv-aflibercept was characterized by a low clearance (0.5 to 3 mL/hr/kg), a low volume of distribution (51 to 77 mL/kg), and a long apparent elimination half-life (t1/2) of 48 to 98 hours. Based on the correlation between exposure and activity in non-clinical models, the target pharmacological exposure in humans is proposed to be a safely administered dose of ziv-aflibercept at which an excess of free ziv-aflibercept is sustained (Investigator's Brochure, 2011).

Clinical overview

The cutoff for data inclusion in this update is 31 July 2011. To date, the clinical development of ziv-aflibercept encompasses a total of 41 clinical oncology trials (25 sanofi trials and 16 national cancer institute [NCI] trials) in more than 3700 cancer patients mostly with advanced solid malignancies as well as 2 clinical trials in 76 healthy subjects (PDY6655 and PDY6656). Doses have been administered up to 800 µg/kg SC twice weekly, 7 mg/kg IV every 2 weeks (q2w), and 9 mg/kg IV every 3 weeks (q3w).

Ziv-aflibercept was initially administered SC in 2 single-agent dose-escalation safety and pharmacokinetic (PK) studies (TED6113/6114) in patients with advanced solid tumors or lymphomas. However, the SC route of administration was discontinued due to the high volume of injection required for the formulated ziv-aflibercept concentration of 25 mg/mL. Subsequently, only IV administration was used in all clinical studies.

Phase 1 single-agent dose escalation studies (TED6115/TED6116) evaluated safety, tolerability, PK and anti-tumor activity in patients with various solid tumor types. Phase 2 single-agent studies were designed to measure the effect of ziv-aflibercept in patients with ovarian cancers (ARD6122, ARD6772, and EFC6125), and non-small-cell lung adenocarcinoma ([NSCLA], ARD6123).

Combination Phase 1 dose-escalation studies were conducted to evaluate safety, PK, and anti-tumor activity in patients with solid malignancies. The recommended Phase 2 dose (RP2D) of ziv-aflibercept was confirmed in these Phase 1 combination studies as 4 mg/kg every 2 weeks (q2w) when combined with chemotherapy administered every 2 weeks, as was initially determined in single-agent studies TED6115/TED6116.

Combination Phase 3 studies' primary objective was efficacy. In these studies, ziv-aflibercept was administered IV over 1 hour at 4 mg/kg q2w or 6 mg/kg q3w depending on the associated chemotherapy schedule.

In the q2w regimen in Phase 1 and Phase 3 combination studies, ziv-aflibercept was combined with standard doses of the following cytotoxic agents: oxaliplatin/5-fluorouracil/leucovorin (FOLFOX4), [TCD6117]), irinotecan/leucovorin/5-fluorouracil (irinotecan/LV5FU2, [TCD6118]), and gemcitabine or gemcitabine and erlotinib (TCD6121), gemcitabine (EFC10547/VANILLA), and irinotecan/5-FU/leucovorin (FOLFIRI, [EFC10262/VELOUR]).

In the q3w regimen in Phase 1 and Phase 3 combination studies, ziv-aflibercept was combined with standard doses of docetaxel (Taxotere®)/cisplatin/5-fluorouracil (TCF, [TCD6119]), docetaxel or docetaxel/cisplatin or pemetrexed (TCD6120), and docetaxel (EFC10261/VITAL).

Clinical pharmacology

Pharmacokinetics measurements were also performed during clinical trials and to characterize the PK of ziv-aflibercept, 2 analytes were quantified in healthy subjects and in patients: free ziv-aflibercept (compound not complexed to VEGF) and bound ziv-aflibercept (VEGF:aflibercept complex in a ratio 1:1). Bound ziv-aflibercept is pharmacologically inert. In addition, population PK analyses were conducted based on pooled PK data from Phase 1, Phase 2 and Phase 3 studies.

Free ziv-aflibercept is thought to be cleared by 2 mechanisms in humans: a fast clearance resulting from binding VEGF to form bound ziv-aflibercept, and a slower pathway where the free ziv-aflibercept is eliminated by other biological mechanisms, such as protein catabolism. The results in humans are consistent with those from animal studies. Renal elimination of ziv-aflibercept has not been investigated in humans. However, since high molecular weight (MW) proteins are not cleared by this route, renal elimination of ziv-aflibercept is expected to be minimal. This has been confirmed in rat studies.

Ziv-aflibercept exhibits a non linear PK with higher clearance at lowest dose levels whilst the PK of free ziv-aflibercept is linear over the 2-9 mg/kg dose range. This could be related to saturable high- affinity binding of ziv-aflibercept to endogenous VEGF at higher doses, limited by VEGF availability. At doses greater than 2 mg/kg, free ziv-aflibercept clearance is 1.0 L/day with a terminal half-life of 6 days and a volume of distribution (Vss=7.8 L) slightly greater than blood compartment. Elimination of VEGF-bound ziv-aflibercept is slower with an apparent clearance of
0.182 L/day and a half-life of 15 days. At 4 mg/kg q2w and 6 mg/kg q3w, concentrations of free ziv-aflibercept were near steady-state levels by the second cycle with essentially no accumulation (accumulation ratio of 1.2 and 1.1, respectively).

According to simulations conducted using the population PK model, at 4 mg/kg q2w, the free to bound ziv-aflibercept ratio exceeds 1 throughout all the dosing intervals for 89% of the population. Consistently, the mean free over bound ziv-aflibercept ratio measured in all studies

showed that free was in excess of bound ziv-aflibercept throughout treatment period at dose levels greater than 2 mg/kg every 2 weeks or greater than 4 mg/kg every three weeks.

In combination therapies, no impact of ziv-aflibercept was observed on the PK of cytotoxic agents including oxaliplatin, cisplatin, 5-FU, irinotecan, docetaxel, pemetrexed, gemcitabine and erlotinib.

Pharmacodynamics (PD) and PK/PD evaluations were also undertaken during clinical trials to determine the effect of ziv-aflibercept on blood pressure (PDY6655 and PDY6656), on the Q-T interval (TES10897), and on the relationship between PK parameters and safety and efficacy variables in Phase 3 studies (EFC10547/VANILLA, EFC10261/VITAL, EFC10262/VELOUR).

The results on blood pressure (BP) from PDY6655 and PDY6656, suggested a renin-independent mechanism of hypertension induced by ziv-aflibercept. No clear mechanism of the dose-related increase in BP was revealed in both studies, in particular, no change in renin angiotensin aldosterone system was observed.

In the randomized, double-blind trial (TES10897) of docetaxel combined with either ziv-aflibercept 6 mg/kg q3w or placebo, it was concluded that ziv-aflibercept 6 mg/kg did not affect the ventricular repolarization in humans to an extent that would require substantial risk-benefit evaluation.

Across the Phase 3 trials, individual free ziv-aflibercept clearance and AUCs were consistently correlated with both clinical efficacy outcomes and some class event safety endpoints. Overall, the lower the free ziv-aflibercept clearance, and the higher the free ziv-aflibercept AUC, the longer the overall survival (OS) and progression-free survival (PFS); but the higher the incidences of hypertension (in each Phase 3 trial) and hemorrhage (in the EFC10262/VELOUR MCRC pivotal Phase 3 trial). Considering these findings and the clinical results of EFC10262/VELOUR, the ziv-aflibercept dose of 4mg/kg q2w appears to correspond to an adequate dose when combined with FOLFIRI in MCRC and for general use in combination therapy.

In clinical studies, serum levels of anti-aflibercept antibodies were measured in all patients during and after treatment. A low incidence of positive responses in the assays was reported and no or limited effect of positive response in the assays was observed on PK.

2.3 Rationale

2.3.1 Rationale for ziv-aflibercept in pNETs

Well-differentiated neuroendocrine tumors (WDNET) can originate from cells scattered throughout the body. While generally thought to be rare, its diagnosed incidence is on the rise.(1) WDNETs are vascular and known to express vascular endothelial growth factor (VEGF).(17, 18) Prior studies with VEGF monoclonal antibody, bevacizumab,(19) and VEGF tyrosine kinase inhibitors sunitinib,(13, 20) sorafenib,(14) and pazopanib(15) have demonstrated promising activity. The response rates for VEGF tyrosine kinase inhibitors have generally been higher for

patients with pancreatic NETs. A recent phase III study reported improved Progression Free Survival (PFS) among patients with advanced pancreatic NET treated with sunitinib compared to placebo.(21)

There is also data to support that PlGF may be of critical importance in pNETs. In RADIANT-3, largest phase III study to have been ever conducted in pNETs, Everolimus significantly improved PFS compared with placebo (11 vs 4.6 months; HR=0.35; 95% CI, 0.27 to 0.45; P<.001).(9) We recently reported the analysis of VEGF pathway biomarkers from the study.(22) In univariate analyses, patients with elevated baseline VEGF-A (P =0.001), PlGF (P =0.004) or sVEGFR1 (P <0.001) had significantly shorter PFS compared to those with low marker levels. In multivariate analysis using a Cox proportional hazards model stratified by treatment arm, which included all baseline angiogenesis markers (high vs low), only sVEGFR1 and PlGF were significantly associated with PFS (HR 1.54 [95% CI, 1.20–1.98; P<0.001] and 1.35 [95% CI, 1.01–1.81; P=0.46] respectively).(22) These analyses suggest PlGF plays a significant role in pNET and there is rationale to study ziv-aflibercept in pNETs.

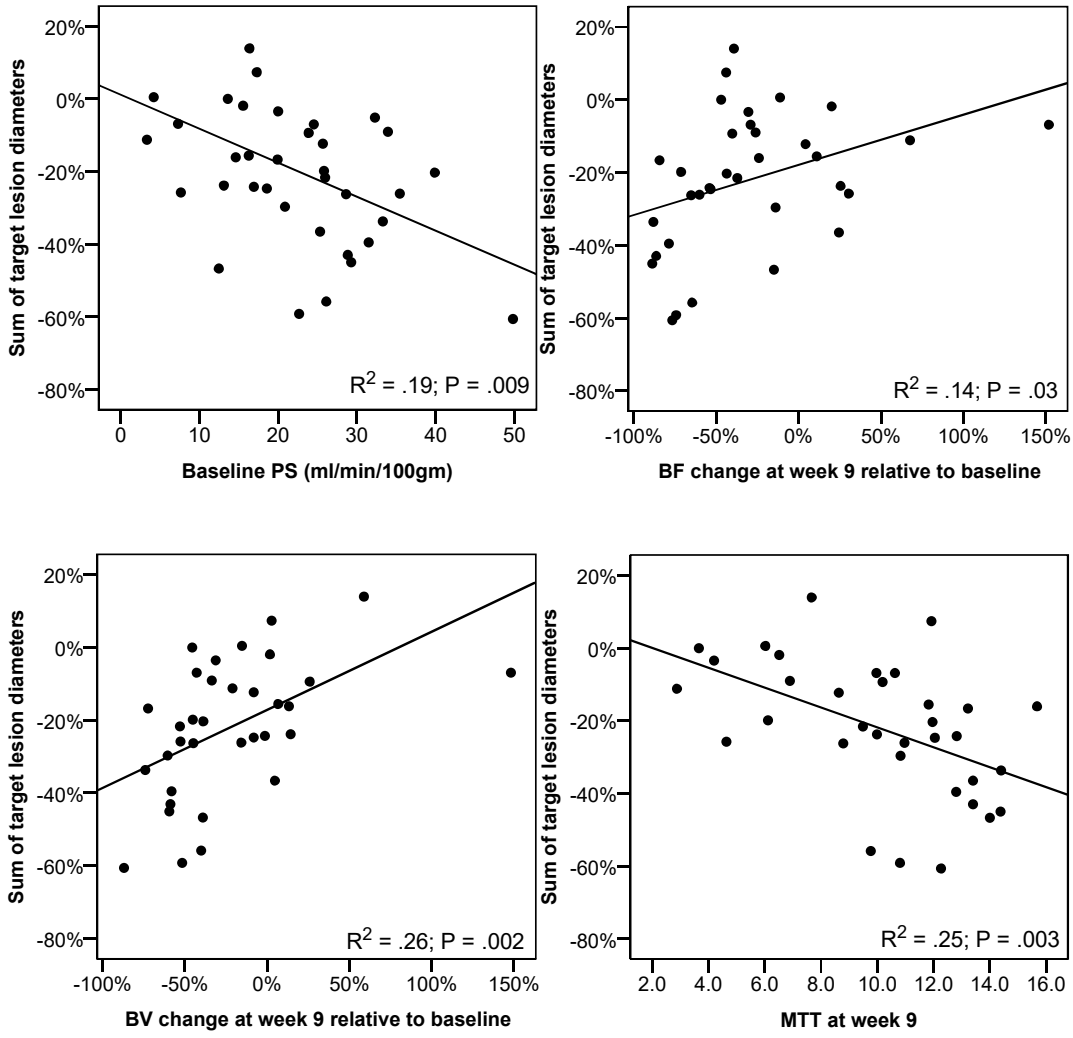
2.3.2 Rationale for baseline perfusion CT as predictive biomarker

There is urgent need for the development of predictive and prognostic biomarker in oncology to accelerate advances in novel therapeutics, and to develop personalized therapy. Biomarkers for therapies targeting angiogenesis have been particularly challenging. This is in part due to fact that tumor response rates with these and other molecularly targeted therapies have generally been low. Nonetheless, treatment can be associated with significant improvements in progression-free survival and overall survival. Predictive, prognostic, and pharmacodynamic biomarkers that will enable development of novel drugs and novel drug combinations targeting angiogenesis are needed.

Since the initial report that a greater reduction in Ktrans, measured by DCE-MRI, was associated with disease stabilization in a phase I study of VEGF tyrosine kinase inhibitor, PTK/ZK,(12) many have attempted to correlate dynamic imaging findings with clinical outcome with varying degrees of success.(4, 13-16) In our prior study with bevacizumab and PEG interferon, perfusion CT (pCT), demonstrated that bevacizumab led to rapid and sustained decrease in tumor blood flow (BF), and suggested that lower post-treatment blood volume (BV) correlated with PFS.(4) One limitation of many past studies, including our prior study,(4) is that dynamic imaging was optional and not uniformly performed among all patients, limiting statistical power and raising the issue of potential selection bias. Other retrospective studies have included heterogeneous groups of patients treated with different VEGF inhibitors. Nonetheless, many of these studies suggested that dynamic imaging has the potential to select patients likely to benefit from anti-angiogenic therapy. (4, 13-16)

In our more recent study with bevacizumab and everolimus, we confirmed that the absolute decrease in tumor BF following bevacizumab and everolimus, correlated with baseline BF, and that such therapy decreased tumor BF by a percentage.(17) In this study, pre-treatment permeability surface (PS), percent reduction in BF, BV, and post-treatment mean transit time (MTT) correlated with RECIST response.(17) Scatter plot of parameters with best change in RECIST target lesion diameters are included below.

Figure 1. Correlation of perfusion CT parameters with best changes RECIST target lesion measurement following treatment with VEGF inhibitors.



The high number of parameters correlating with outcome is likely related to the high degree of correlation between these parameters. In a recent pooled-analysis of pancreatic NET patients treated with VEGF inhibitors at MD Anderson, baseline BV also correlated with response. Of particular interest are the correlations between pre-treatment BV and PS with tumor response. This suggests that one can select patient likely to benefit from anti-angiogenic therapy based on one pre-treatment scan. We will formally test this hypothesis in the current study.

If the pCT can be confirmed to select patients who will benefit from VEGF inhibitors such as ziv-aflibercept, this approach could be used for further development of ziv-aflibercept in NET as well, as identification of subgroups of patients with other solid tumors likely to benefit from agents targeting the VEGF pathway.

2.4 Correlative Studies Background

See section 2.3.2. As perfusion CT is co-study primary objective, background is described in above section.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed low or intermediate grade pancreatic NET. Patients with neuroendocrine tumors associated with MEN1 syndrome will be eligible.

3.1.2 Patients must have unresectable or metastatic disease.

3.1.3 Patients must have at least one measurable site of disease according to RECIST 1.1 that has not been previously irradiated.

3.1.4 Patients must have at least one lesion suitable for perfusion CT. The lesion should be greater than or equal to 3 cm in size in the cranial caudal direction.

3.1.5 Patient must have no contraindication for CT with iodinated contrast

3.1.6 Patients who are on a somatostatin analogue for control of hormonal syndromes must be on a stable dose (no change in mg dose of long acting octreotide or lanreotide, changes in dosing interval of +/- 1 week is allowed) for 2 months prior to date of study entry.

3.1.7 Women of child-bearing potential must have a negative serum pregnancy test within 7 days prior to date of study entry. Women who have had menses within the past 2 years, who have not had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy are considered to be of child-bearing potential. Patients with elevated hCG at baseline that is judged to be related to the tumor are eligible if hCG levels do not show the expected doubling when repeated 5-7 days later, or pregnancy has been ruled out by vaginal ultrasound.

3.1.8 Any number of prior lines of systemic anti-neoplastic therapy are allowed. Treatment with ≤ 1 prior VEGF inhibitor will be allowed.

3.1.9 Patients must have normal organ and marrow function as defined below:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	≤1.5 × institutional upper limit of normal
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal
– creatinine	within normal institutional limits
	OR

– creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.
– Urine protein:creatinine ratio	≤ 1.0.
	OR
– 24-hour urine protein	≤ 500 mg (24-hour total urine protein only need be obtained if urine protein : creatinine ratio < 1.0)

3.1.10 Patients must have PT/INR/PTT within 1.2 X the upper limit of normal.

3.1.11 Patients must have resting blood pressure (BP) no greater than 140 mmHg (systolic) or 90 mmHg (diastolic) for eligibility. Initiation or adjustment of BP medication is permitted prior to study entry.

3.1.12 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Less than 28 days elapsed from prior radiotherapy, from prior surgery and prior chemotherapy to the time of randomization. Less than 42 days elapsed from prior major surgery to the time of randomization.

3.2.2 Adverse events (with exception of alopecia, peripheral sensory neuropathy and those listed in specific exclusion criteria) from any prior anti cancer therapy of grade >1 (National Cancer Institute Common terminology Criteria [NCI CTCAE] v.4.0).

3.2.3 Age < 18 years.

3.2.4 ECOG PS > 2.

3.2.5 History of brain metastases, uncontrolled spinal cord compression, or carcinomatous meningitis or new evidence of brain or leptomeningeal disease.

3.2.6 Other prior malignancy. Adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix or any other cancer from which the patient has been disease free for > 5 years are allowed.

3.2.7 Participation in another clinical trial and any concurrent treatment with any investigational drug within 30 days prior to study entry.

3.2.8 Any of the following within 6 months prior to study entry: myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, NYHA class III or IV congestive heart failure, stroke or transient ischemic attack.

3.2.9 Any of the following within 3 months prior to study entry: Grade 3-4 gastrointestinal bleeding/hemorrhage, treatment resistant peptic ulcer disease, erosive oesophagitis or gastritis, infecttious or inflammatory bowel disease, diverticulitis, pulmonary embolism or other uncontrolled thromboembolic event.

3.2.10 Occurrence of deep vein thrombosis within 4 weeks, prior to study entry.

3.2.11 Acquired immuno deficiency syndrome (AIDS-related illnesses) or known HIV disease requiring antiretroviral treatment.

3.2.12 Any severe acute or chronic medical condition, which could impair the ability of the patient to participate to the study or to interfere with interpretation of study results.

3.2.13 Pregnant or breast feeding women. Positive pregnancy test (serum or urine β-HCG) for women of reproductive potential.

3.2.14 Patient with reproductive potential (female and male) who do not agree to use an accepted effective method of contraception (hormonal or barrier methods, abstinence) during the study treatment period and for at least 3 months following completion of study treatment. For female patient enrolled, the following methods of contraception are acceptable: oral contraceptives accompanied by the use of a second method of contraception, as it is not known how oral contraceptives interact with all study medications or Intra Uterine Device (IUD) or women who are surgically sterile, or women who are post –menopausal or other reasons have no chance of becoming pregnant.

3.2.15 Absence of signed and dated Institutional Review Board-approved patient informed consent from prior to enrollment in the study.

Exclusion criteria related to ziv-aflibercept:

3.2.16 Urine protein-creatinine ratio (UPCR) >1 urinalysis or total urine protein > 500 mg/24h.

3.2.17 Serum creatinine > 1.5 x upper limit of normal (ULN). If creatinine 1.0-1.5 x ULN, creatinine clearance, calculated according to Cockroft-Gault formula, < 60 ml/min will exclude the patient.

3.2.18 History of uncontrolled hypertension, defined as systolic blood pressure > 150 mmHg while simultaneous diastolic blood pressure >100 mmHg, or systolic blood pressure >180 mmHg when diastolic blood pressure < 90 mmHg, on at least 2 repeated determinations on separate days within 3 months prior to study enrollment.

3.2.19 Patients on anticoagulant therapy with unstable dose of warfarin and/or having an out-of-therapeutic range INR (>3) within the 4 weeks prior to study entry.

3.2.20 Evidence of clinically significant bleeding diathesis or underlying coagulopathy (e.g. INR>1.5 without vitamin K antagonist therapy), non-healing wound.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study centrally at the MD Anderson Cancer Center (Coordinating Center) by the Study Coordinator. The required forms Registration Form can be found in Appendix D.

Following registration, patients should begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

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

4.2 Registration Process

To register a patient, the following documents should be completed by the research nurse or data manager and faxed *713-563-9188* or e-mailed mebrimer@mdanderson.org to the Study Coordinator:

- Copy of required laboratory tests
- Signed patient consent form
- HIPAA authorization form
- Registration Form)

The research nurse or data manager at the participating site will then call *713-563-9188* or e-mail mebrimer@mdanderson.org the Study Coordinator to verify eligibility. To complete the registration process, the Coordinator will

- assign a patient study number
- register the patient on the study
- assign the patient a dose
- fax or e-mail the patient study number and dose to the participating site

- call the research nurse or data manager at the participating site and verbally confirm registration.

5. TREATMENT PLAN

One cycle consists of 21 days (3 weeks). See section 10.0 for acceptable window for testing and treatment. Ziv-aflibercept will be given intravenously on day 1 of each cycle. Treatment response will be evaluated every 3 cycles (approximately 9 weeks depending on any treatment delays).

Perfusion CT will be performed at baseline (pre-treatment), cycle 1 day 21 (± 2 days, prior to cycle 2 dose), and at time of progression. The progression perfusion CT will not be performed if > 28 days have elapsed from the last ziv-aflibercept treatment (i.e. canceled or delayed treatment due to adverse event).

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description					
Agent	**Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Ziv-aflibercept	SBP must be ≤140 and DBP must be ≤90 prior to administration	6 mg/kg at concentration of .06 – 8 mg/mL. Ziv-aflibercept will be diluted in NS	IV over 60 minutes (up to 120 minutes is permitted and not considered a deviation).	Days 1	21 days (3 weeks)

Management of Hypersensitivity Reactions: Stop infusion of Ziv-aflibercept for 30-60 minutes. Medicate with diphenhydramine 25 – 50 mg IV (or a similar antihistamine) and steroids such as hydrocortisone 50-100 mg IV or dexamethasone 10-20 mg IV approximately 30 minutes before re- starting the ziv-aflibercept. If the subject re-develops a hypersensitivity reaction despite treatment with diphenhydramine and steroids, the infusion should be stopped for another 30 – 60 minutes, depending upon the severity of the reaction. The infusion may be resumed by administering a histamine H2-receptor antagonist approximately 30 minutes before restarting the ziv-aflibercept infusion and meperidine 25-50 mg IV if patient still had chills and rigors. Famotidine 20 mg IV or ranitidine 50 mg IV are recommended rather than cimetidine because of the lack of likely metabolic/pharmacologic interactions with the former drugs. The rate of the ziv-aflibercept infusion may also be slowed from 60 minutes to 2 hours. Also, it is

permissible to premedicate overnight with steroids such as dexamethasone or prednisone. All subjects should be monitored while receiving the ziv-aflibercept infusion and emergency medical equipment and health care personnel must be readily available to respond to hypersensitivity reactions or other medical emergencies.

5.2 General Concomitant Medication and Supportive Care Guidelines

Use of somatostatin analogues for the control of hormone related syndrome from neuroendocrine tumors is allowed. Both Octreotide LAR at doses of ≤30 mg IM every 3 to 4 weeks, and Lanreotide autogel ≤120 mg SC every 3 to 4 weeks can be used as long acting agent. Octreotide short-acting SC 2 – 4 times per day can also be used for supplemental therapy

The use of interferon or everolimus for control of hormonal syndrome is not allowed.

Other medications used for the supportive therapy of hormonal syndrome are allowed. 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.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.4 Duration of Follow Up

Patients removed from study without progression will be followed until progression, start of new anti-neoplastic therapy, withdrawal of consent, or death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

For continuation treatment during subsequent cycles, patient should have recovered from any G3 or G4 treatment-related AEs to ≤G1. With exception of ziv-aflibercept doses withheld for proteinuria, the maximum delay for subsequent cycles is 4 weeks from when treatment was originally due (7 weeks from last dose). If a dose is delayed beyond 4 weeks for any reason other than proteinuria, patient will permanently discontinue therapy. Please see Table 3 for dose modification and interruptions due to proteinuria.

Patients should be permanently discontinued for the following AEs:

- Severe (G3 or G4) hemorrhage
- Gastrointestinal perforation
- Compromised wound healing (non-healing wounds)
- Fistula formation
- Hypertensive crisis or hypertensive encephalopathy (G4 hypertension)
- Arterial thromboembolic events (any grade)
- Nephrotic syndrome or thrombotic microangiopathy (TMA)
- Reversible posterior leukoencephalopathy syndrome (RPLS)

Temporarily hold ziv-aflibercept therapy for the following:

- Elective surgery should be carried out at least 4 weeks after last dose of ziv-aflibercept. Do not resume ziv-aflibercept for at least 4 weeks following major surgery and until the surgical wound is fully healed.
- For minor surgery such as central venous access port placement, biopsy, and tooth extraction, ziv-aflibercept may be initiated/resumed once the surgical wound is fully healed.

Dose modification

Ziv-aflibercept doses will be modified according to the dose level described in Table 1. Only one dose reduction is permitted.

Table 1 – Ziv-aflibercept dose reduction level

	Initial dose (mg/kg)	Dose reduction, level - 1 (mg/kg)

Ziv-aflibercept	6	3

Actions to be taken for ziv-aflibercept according the type of toxicity are described in Table 2, Table 3 and Table 4.

Table 2 – Dose modifications for ziv-aflibercept

Toxicity	Grade	Action to be taken
Hypertension	Grade ≤ 2	Initiate antihypertensive drug therapy (see recommendation below) and close monitoring of BP for further adjustment, as needed. No dose modification and no delay.
	Grade 3 (resting systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg, and requiring more than one drug or more intensive therapy than previously***)	Modify antihypertensive drug therapy (see recommendation below). Delay the administration of ziv-aflibercept, for a maximum of 4 weeks, until recovery to blood pressure (BP) ≤150/100 or to systolic BP < 180 if diastolic BP < 90 for patients with known history of isolated systolic hypertension: • If BP is controlled within 2 weeks delay: o First episode: readminister ziv-aflibercept at the same dose. o Second episode: readminister ziv-aflibercept, with ziv-aflibercept reduced to dose level-1. o Third episode, discontinue ziv-aflibercept. • If BP is still uncontrolled despite appropriate anti hypertensive treatment and after 2 - 4 weeks delay: Ziv-aflibercept will be reduced to dose level -1. • In case of re-occurence of grade 3 BP despite dose reduction of ziv-aflibercept, or if BP is still uncontrolled despite delay of 4 weeks, the patients will be permanently discontinued from ziv-aflibercept.
	Grade 4	Permanently discontinue study treatment
Arterial thromboembolic events (e.g.: myocardial infarction, or stroke…) documented by appropriate tests	Grade 3-4	Permanently discontinue study treatment
Hemorrhage	Grade 3-4	Permanently discontinue study treatment
GI perforation/ fistula formation	Any Grade	Permanently discontinue study treatment
Reversible posterior Leuko- encephalopathy syndrome documented with appropriate tests	Any Grade	Permanently discontinue study treatment
Venous Thromboembolic	Grade 3 (DVT)	First episode: Treat DVT with heparins and continue study treatment*

Toxicity	Grade	Action to be taken
Event documented by appropriate tests		Second episode despite appropriate anticoagulation: Permanently discontinue ziv-aflibercept
	Grade 4 (PE)	Permanently discontinue study treatment**

* Based on investigator's judgement in assessing potential risk of extesion and/or embolization.
** Continuation of ziv-aflibercept may be considered, depending on individual benefit/risk assessment in case of incidental discovery of asymptomatic pulmonary embolism.
*** Initial titration of anti-hypertensive medication following the start of a new drug (eg terazosin or calcium channel blocker) will not count as more intensive therapy.

Hypertension therapy recommendations:

- *For patients without prior antihypertensive therapy*, at the time of the hypertensive episode the initiation of calcium-channel blockers should be considered as a first-intent treatment. A close monitoring of the BP should be initiated for further adjustment in treatment, as needed. Ultimately, antihypertensive treatment must be individualized based on the presence of comorbidity factors such as diabetes, cardiovascular or renal disease, additionally taking into account the safety and the efficacy of any prior antihypertensive therapy received. In addition, oral and/or intravenous sodium intake should be carefully monitored in these patients.
- *For patients already under anti-hypertensive therapy* efforts should be done to optimize the existing therapy before adding other agents as required to control the BP.

When hypertension is accompanied by signs or symptoms of end organ damage such as hypertensive retinopathy, kidney function abnormalities (like progressive proteinuria), or any signs or symptoms of cardiovascular morbidity or central nervous system (CNS) morbidity, treatment with ziv-aflibercept should be interrupted.

Proteinuria:

Determination and management of proteinuria:
Prior to each administration of ziv-aflibercept, perform an UPCR.

Urinary protein creatinine ratio (UPCR) corresponds to the ratio of urinary protein and urinary creatinine concentrations (expressed in mg/dL). There is a high correlation between morning UPCR and 24-hour proteinuria in patients with normal or reduced renal function, UPCR demonstrated very good to excellent performance for the diagnosis of both abnormal and nephrotic proteinuria at all renal function levels. This ratio provides an accurate quantification of 24-hours urinary protein excretion.

UPCR to detect proteinuria, will be done on morning urine spot. If UPCR > 1, 24-hour urine collection to grade proteinuria will be performed. In addition, in case proteinuria is associated with hematuria (microscopic or macroscopic), schistocytes, orosomucoïd, haptoglobin, and LDH will be measured in blood and a nephrologist advice should be considered as detailed in Table 3.

Proteinuria should always be assessed taking into account the presence or absence of

hematuria and the blood pressure status of the patient.

Table 3 summarizes the course of action with regard to ziv-aflibercept dosing, which will depend on the presence of hematuria and the level of 24h proteinuria results. Only one dose level reduction is permitted for ziv-aflibercept.

Table 3 – Management of proteinuria

Prior to cycle n ziv-aflibercept administration	Ziv-aflibercept dosing for cycle n	During cycle n Repeat 24h proteinuria as necessary*	Ziv-aflibercept dosing for cycle n +1	During cycle n +1 Repeat 24h proteinuria as necessary*	Ziv-aflibercept dosing for cycle n + 2
UPCR [0-1]	Dose aflibercept	-	-	-	-
UPCR [1-2] Absence of hematuria	Dose, then perform 24h proteinuria:				
	if ≤3.5g/24h	≤2g/24h prior n+1 dosing	Dosing ziv-aflibercept	-	-
		>2g/24h prior n+1 dosing	Omit dosing ziv-aflibercept	≤2g/24h prior n+1dosing	Resume ziv-aflibercept level -1**
				>2g/24h prior n+1 dosing	Permanently discontinue aflibercept
	if > 3.5g/24h	≤2g/24h prior n+1 dosing	Dosing ziv-aflibercept level -1**	-	-
		>2 ≤ 3.5g/24h prior n+1 dosing	Omit dosing ziv-aflibercept	≤2g/24h prior n+1 dosing	Resume ziv-aflibercept level -1**
				>2g/24h prior n+1 dosing	Permanently discontinue aflibercept
		>3.5g/24h prior n+1 dosing	Permanently discontinue ziv-aflibercept		
UPCR [1-2] Presence of hematuria Or UPCR >2	Omit dosing aflibercept	Full nephrologic work-up and seek nephrologist opinion			
		TMA ruled out and ≤2g/24h prior n+1 dosing	Dosing ziv-aflibercept	-	-
		TMA ruled out and >2 ≤ 3.5g/24h prior n+1 dosing	Omit dosing ziv-aflibercept	≤2g/24h prior n+1 dosing	Resume ziv-aflibercept level -1**
				>2g/24h prior n+1 dosing	Permanently discontinue ziv-aflibercept
		TMA ruled out and >3.5g/24h prior n+1 dosing***			
		TMA diagnosed	Permanently discontinue ziv-aflibercept, seek nephrologist opinion		
Nephrotic syndrome	Permanently discontinue ziv-aflibercept, perform nephrologic work-up, seek nephrologist opinion for continuation of chemotherapy				

TMA: Thrombotic micro-angiopathy
*Patient can be monitored with UPCR as necessary, however 24h proteinuria should be performed prior to make dosing decision.
** When patient is already treated at dose level -1, ziv-aflibercept should be discontinued.

Reversible posterior leuko-encephalopathy (RPLS) or clinical symptoms related to vasogenic edema of the white matter:

Clinical presentations are variable and may include headache, altered mental status, seizure and cortical visual deficit. Hypertension is a risk factor. MRI scans are key to diagnosis and typically demonstrate vasogenic edema (hyperintensity in T2 and FLAIR images and hypodensity in T1 images) predominently 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 with early recognition of symptoms and timely correction of the underlying causes, including control of BP and interruption of the offending drug, which are important in order to prevent progression to irreversible tissue damage.

Gastro-intestinal perforation:

In case a patient reported abdominal pain or increase in severity of pre-existing abdominal pain, with or without associated symptoms (such as nausea, vomiting, constipation), he/she should be evaluated by a physician for possible gastro-intestinal perforation, as this has been reported with anti-VEGF agents.

Hypersensitivity reaction:

In case of hypersensitivity reaction, institutional treatment guidelines for this type of AEs, or the following proposed guideline in Table 4 can be applied.

Table 4 – Acute infusion reaction management

Symptom Severity	Intervention Recommendation
Mild-Moderate E.g., NCI CTCAE grade ≤ 2 cutaneous reaction, pruritus, flushing, rash, dyspnea, tachycardia, hypotension, anxiety, headache, myalgias, edema, nausea	Stop ziv-aflibercept infusion; Give diphenhydramine 50 mg IV and/or IV dexamethasone 10 mg; Resume ziv-aflibercept infusion after subject recovery.
Severe e.g., symptomatic bronchospasm, generalized urticaria, systolic BP ≤ 80 mm Hg, angioedema, anaphylaxis	Stop ziv-aflibercept infusion; Give IV diphenhydramine 50 mg and/or IV dexamethasone 10 mg and/or epinephrine as needed; Permanently discontinue ziv-aflibercept.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Ziv-aflibercept (VEGF-Trap, AVE 0005, NSC 724770)

The Comprehensive Adverse Events 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 941 patients.* Below is the CAEPR for Ziv-aflibercept (VEGF-Trap, AVE 0005).

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

Version 2.7, October 2, 2017[1]

Adverse Events with Possible Relationship to Ziv-aflibercept (VEGF-Trap, AVE 0005) (CTCAE 4.0 Term) [n= 941]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
		Febrile neutropenia	
		Hemolytic uremic syndrome	
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Cardiac disorders - Other (intracardiac thrombus)	
		Chest pain - cardiac	
		Myocardial infarction	
		Restrictive cardiomyopathy	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***

Adverse Events with Possible Relationship to Ziv-aflibercept (VEGF-Trap, AVE 0005) (CTCAE 4.0 Term) [n= 941]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Gastrointestinal fistula[2]	
		Gastrointestinal perforation[3]	
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Pain		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Wound complication		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		
	Creatinine increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
Headache			***Headache (Gr 3)***
		Ischemia cerebrovascular	***Ischemia cerebrovascular (Gr 2)***
		Reversible posterior leukoencephalopathy syndrome	
		Transient ischemic attack	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
Proteinuria			***Proteinuria (Gr 3)***
		Renal and urinary disorders - Other (nephrotic syndrome)	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
	Genitourinary system fistula[4]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***

Adverse Events with Possible Relationship to Ziv-aflibercept (VEGF-Trap, AVE 0005) (CTCAE 4.0 Term) [n= 941]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dyspnea		***Dyspnea (Gr 3)***
	Respiratory, thoracic and mediastinal disorders - Other (rhinorrhea)		
Voice alteration			***Voice alteration (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Palmar-plantar erythrodysesthesia syndrome		
	Skin hyperpigmentation		
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 3)***
	Vascular disorders - Other (hemorrhage)[5]		***Vascular disorders - Other (hemorrhage)[5] (Gr 4)***

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

[2]Gastrointestinal fistulas may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[4]Genitourinary fistulas may include: female genital tract fistula, uterine fistula, and vaginal fistula.

[5]The majority of hemorrhage events were mild. Major events, defined as symptomatic bleeding in a critical area or organ (e.g., eye, GI hemorrhage, GU hemorrhage, respiratory hemorrhage), and nervous system [including fatal intracranial hemorrhage and cerebrovascular accident] have been reported.

[6]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on Ziv-aflibercept (VEGF-Trap, AVE 0005) trials but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ziv-aflibercept (VEGF-Trap, AVE 0005) caused the event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (hemoglobin increased); Hemolysis
CARDIAC DISORDERS - Acute coronary syndrome; Cardiac disorders - Other (left ventricular diastolic dysfunction); Heart failure; Left ventricular systolic dysfunction; Pericarditis; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus; Vertigo
ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism

EYE DISORDERS - Blurred vision; Extraocular muscle paresis; Eye disorders - Other (blindness transient);
Eye disorders - Other (diplopia); Vitreous hemorrhage
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal mucositis; Colitis; Dental caries; Dry mouth; Dyspepsia; Dysphagia; Esophageal pain; Flatulence; Gastritis; Gastrointestinal disorders - Other (early satiety); Gastrointestinal disorders - Other (eructation); Gastrointestinal disorders - Other (gastrointestinal necrosis); Gastrointestinal disorders - Other (hiatal hernia); Gastrointestinal disorders - Other (intestinal ischemia); Gastrointestinal disorders - Other (peritonitis); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gingival pain; Hemorrhoids; Ileus; Oral pain; Rectal mucositis; Rectal ulcer; Small intestinal mucositis; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema trunk; Facial pain; Infusion related reaction; Injection site reaction; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Cholecystitis
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Infection[6]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Biliary anastomotic leak; Gastric anastomotic leak; Vascular access complication; Wound dehiscence
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; Cardiac troponin I increased; Ejection fraction decreased; GGT increased; Investigations - Other (elevated LDH); Lipase increased; Serum amylase increased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Avascular necrosis; Back pain; Chest wall pain; Generalized muscle weakness; Head soft tissue necrosis; Joint range of motion decreased; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (ischemic avascular osteonecrosis); Musculoskeletal and connective tissue disorder - Other (muscle spasms); Musculoskeletal and connective tissue disorder - Other (musculoskeletal stiffness); Musculoskeletal and connective tissue disorder - Other (rotator cuff tear); Myositis; Neck pain; Osteonecrosis of jaw; Pain in extremity; Pelvic soft tissue necrosis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)- Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage)
NERVOUS SYSTEM DISORDERS - Amnesia; Ataxia; Cognitive disturbance; Dizziness; Dysgeusia; Encephalopathy; Extrapyramidal disorder; Leukoencephalopathy; Memory impairment; Paresthesia; Peripheral sensory neuropathy; Seizure; Syncope; Vagus nerve disorder
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia; Psychiatric disorders - Other (mental status change); Psychosis
RENAL AND URINARY DISORDERS - Hematuria
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Hoarseness; Hypoxia; Laryngeal mucositis; Nasal congestion; Pharyngeal mucositis; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary fibrosis; Respiratory, thoracic and mediastinal disorders - Other (nasal dryness); Respiratory, thoracic and mediastinal disorders - Other (septal perforation); Respiratory, thoracic and mediastinal disorders - Other (throat swelling); Respiratory, thoracic and mediastinal disorders - Other (tracheal fistula); Tracheal mucositis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Nail loss; Rash acneiform; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (hyperemia); Skin ulceration
VASCULAR DISORDERS - Hematoma; Hypotension; Peripheral ischemia; Phlebitis

Note: Ziv-aflibercept (VEGF-Trap, AVE 0005) 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.

7.1.1 Adverse Event List(s) for CIP (*e.g.* Study-Specific) Commercial Imaging Agents

Commercial standard iodinated contrast agent will be used for perfusion CTs performed in this study. Known adverse events associated with iodinated contrast agents include: hot flashes3.4%; angina pectoris 3.0%; flushing 1.8%; bradycardia 1.3%; hypotension 1.0%; hives 1.0%.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 *The following text is required for multi-institutional studies only and may be deleted for single institution studies.*
CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal

Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

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.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

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

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

FOR USE IN CIP STUDIES INVOLVING COMMERCIAL (NON-IND/IDE) AGENTS ONLY

CIP Commercial Agent Studies: Expedited Reporting Requirements for Adverse Events that Occur in a CIP Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Imaging Agent [1, 2]

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="3">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

[2] For studies using PET or SPECT agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

8. PHARMACEUTICAL AND/OR IMAGING AGENT INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s)

8.1.1 Ziv-aflibercept (NSC #724770)

Other Names: VEGF Trap, AVE0005

Classification: Recombinant humanized fusion protein (Chinese hamster ovary source).

M.W.: 115 kDa

Approximate Solubility: at least 100mg/ml water (with 5 mM Na phosphate, 5 mM Na citrate, 100 mM NaCl, 0.004-0.08% Polysorbate 20) at 5°C and 25°C.

Mode of Action: The cytokine VEGF binds to and activates VEGFR1 and VEGFR2 on the vascular endothelium, promoting new vessel formation. VEGF Trap is a soluble recombinant decoy receptor that binds and inactivates extravascular and hematologic VEGF. It reduces tumor vasculature density, available nutrient supply, and tissue matrix components escaping from leaky tumor vessels.

Description: The fusion protein VEGF Trap is 2 portions of human VEGF receptors extracellular domains, VEGFR1 and VEGFR2, fused to the Fc portion of human IgG1.

How Supplied: VEGF Trap is supplied by Sanofi-Aventis Pharmaceuticals and distributed by the CTEP, DCTD, NCI. VEGF Trap is a sterile, nonpyrogenic, colorless to pale yellow solution in vials of 100 mg (4 mL) or 200 mg (8 mL) at a concentration of 25 mg/mL. The solution contains the following excipients: sucrose, sodium chloride, sodium citrate dihydrate, citric acid monohydrate, polysorbate 20, sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, and water for injection. The pH of VEGF Trap is 6.2. The product is packaged in a type 1, clear borosilicate glass vial closed with a flanged cap with tear-off lid and inserted sealing disc, Flurotec® (PTFE) coated.

Preparation: Prior to infusion, the VEGF Trap dosage form must be diluted directly into infusion bags of 0.9% sodium chloride solution. The concentration of the diluted solution can range between 0.6 and 8 mg/mL. The pH of the diluted solution is about 6.2.

Storage: Store intact vials in the refrigerator (2° to 8° C).

Stability: Shelf life stability studies of intact vials are ongoing. VEGF Trap's provisional shelf-life is up to 36 months at 2° to 8°C.

Caution: The sterile single use vials contain no antibacterial preservatives. Discard remaining agent 8 hours after initial entry.

VEGF Trap diluted to a concentration of 0.6 to 8 mg/mL in 0.9% NaCl has demonstrated chemical and physical stability for up to 24 hours under refrigerated conditions (2 to 8°C) or up to 8 hours at ambient temperature (approximately 25°C) in infusion bags made of polyvinyl chloride (PVC) containing di(2-ethylhexyl)phthalate (DEHP) or polyolefin (PVC free DEHP free).

Route of Administration: Intravenous

Method of Administration: Administer VEGF Trap intravenously over 1 hour into a peripheral vein or central venous catheter using gravity, an infusion pump, or syringe pump. The infusion should not exceed two hours at room temperature (approximately 25°C).

VEGF Trap may be administered using infusion tubing made of PVC containing DEHP, polyethylene lined PVC, DEHP free PVC containing tris (2-ethylhexyl) trimellitate (TOTM), polypropylene, or polyurethane.

The infusion set must contain a 0.2 micron polyethersulfone inline filter. Polyvinylidene fluoride (PVDF) filters or Nylon filters should **not** be used.

Availability

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

Ziv-aflibercept is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 Agent Ordering and Agent Accountability

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

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent

Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.1.2.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

There is urgent need for the development of predictive and prognostic biomarker in oncology to accelerate advances in novel therapeutics, and to develop personalized therapy. Biomarkers for therapies targeting angiogenesis have been particularly challenging. This is in part due to the fact that tumor response rates with these and other molecularly targeted therapies have generally been low. Nonetheless, treatment can be associated with significant improvements in progression-free survival and overall survival. Predictive, prognostic, and pharmacodynamic biomarkers that will enable development of novel drugs and novel drug combinations targeting angiogenesis are needed.

Since the initial report that a greater reduction in K^{trans}, measured by DCE-MRI, was associated with disease stabilization in a phase I study of VEGF tyrosine kinase inhibitor, PTK/ZK,(12) many have attempted to correlate dynamic imaging findings with clinical outcome with varying degrees of success.(4, 13-16) In our prior study with bevacizumab and PEG interferon, perfusion CT (pCT), demonstrated that bevacizumab led to rapid and sustained decrease in tumor blood flow (BF), and suggested that lower post-treatment blood volume (BV) correlated with PFS.(4) One limitation of many past studies, including our prior study,(4) is that dynamic imaging was optional and not uniformly performed among all patients limiting statistical power and raising the issue of potential selection bias. Other retrospective studies have included heterogeneous groups of patients treated with different VEGF inhibitors. Nonetheless, many of these studies suggested that dynamic imaging had potential to select patients likely to benefit from anti-angiogenic therapy.(4, 13-16)

In our more recent study with bevacizumab and everolimus, we confirmed that the absolute decrease in tumor BF following bevacizumab and everolimus, correlated with baseline BF, and that such therapy decreased tumor BF by a percentage.(17) In this study, pre-treatment permeability surface (PS), percent reduction in BF, BV, and post-treatment MTT correlated with RECIST response.(17) In a recent pooled-analysis of pancreatic NET patients treated with VEGF inhibitors at M. D. Anderson, baseline BV also correlated with response.

Of particular interest are the correlations between pre-treatment BV and PS with tumor response.

This suggests that one can select patients likely to benefit from anti-angiogenic therapy based on one pre-treatment scan. We will formally test this hypothesis in the current study.

9.1 Perfusion CT

9.1.1 Perfusion CT Procedure and image acquisition

Perfusion CTs will be performed at:

1. Pre-treatment baseline (within 1 week of cycle 1 day 1)
2. Cycle 1 day 21 (+/- 3 days)
3. Time of radiologic disease progression (if patient is ≤ 28 days from last dose of Ziv-aflibercept)

Given the type of tumor studied, it is anticipated that most tumor lesions studied will be located in the liver, but any tumor location can also be studied. Scans will be obtained with patients in the supine position on a 32 or 64-row multidetector CT scanner. Axial cine scans will be performed using a single level of 4 cm thickness at the midpoint of the selected target lesion. CT data will be collected in two phases to cover 4 cm axial thickness through the midpoint of the selected target lesion: there will be an initial 30-40 second breath hold cine acquisition, followed by intermittent breath hold short helical scans extending out to 600 seconds. Data acquisition will start approximately 5 seconds after intravenous injection of 50 mL of a nonionic contrast agent (ioversol [Optiray™] or equivalent,, 320-350 mg of iodine/100 mL, Mallinckrodt Inc., St Louis, MO) using an automatic injector at 7 mL/second, through an 18-gauge needle placed in an antecubital vein. The initial first phase cinecine images, eight contiguous slices each of 5 mm thickness, will be acquired in cine mode with a 1 second rotation speed, and will be reconstructed at the CT console at half rotation intervals, giving an effective temporal resolution of 0.5 seconds; the second phase intermittent short helical images will be anatomically registered with the cine images.

9.1.2 Perfusion CT image analyses

The images will be analyzed centrally at M.D. Anderson using CT-perfusion software on a workstation (CT Perfusion version 3 or higher, Advantage Windows 4.2; GE Medical Systems, Milwaukee, WI). This uses a deconvolution physiological model.(29) A region of interest (ROI) will be placed in the largest available artery in the cine sections, typically the abdominal aorta, which providesprovides the arterial input function for generation of perfusion maps, using the Body Perfusion protocol. In the case of liver lesions, the Liver Perfusion protocol will be used where possible; this utilizes a dual vascular input, consisting of arterial and portal vein inputs. ROIs will be drawn freehand around the periphery of target lesions with reference to the source cine CT images and perfusion parametric maps, on each axial section in which tumor was visualized. This will generate mean BF, BV, MTT, and PS (and in the case of Liver Protocol, also hepatic arterial fraction (HAF)) values for each tumor ROI on each level. The pCT parameter values obtained for each level were then averaged for each lesion evaluated.

9.1.3 Perfusion CT data analyses

See Statistical Section for the analyses of study primary endpoints.

For perfusion CT exploratory endpoints, descriptive statistics will be provided with confidence intervals where appropriate. To explore optimal cut-points for perfusion CT parameters in predicting response, response rate for each parameter with cut-off set at median of the parameter will be computed. In addition, receiver operating characteristic curve will be used to graph the effect of cut-points in perfusion CT parameters on RECIST response classified as a binary outcome.

9.2 Laboratory Correlative Studies

9.2.1.1 **Baseline plasma VEGF-A & PlGF**

We recently reported the analysis of VEGF pathway biomarkers from RADIANT-3, the largest phase III study to have been ever conducted in pNETs.(9, 22) In univariate analyses, patients with elevated baseline VEGF-A (P =0.001), or PlGF (P =0.004) had significantly shorter PFS compared to those with low marker levels. We plan to analyze baseline levels in current study and correlate with outcome as well as baseline perfusion CT parameters.

PlGF levels will be obtained by the R&D Quantikine Human PlGF Immunoassay (#DPG00) and analyzed on a BioTek Synergy HT Multi-detection microplate reader, and analyzed on Gen5 software (BioTek Winooski, Vermont). All samples will be analyzed in duplicate, and each plate will contain positive and negative controls. The assay requires 200 µL of plasma for a duplicated analysis. The lower limits of detection is 7pg/ml, with upper limit for the assay of 1,000 pg/mL. Intra-assay precision is <10%. The variance of the duplicate samples will be determined, and analytes with %CV >15% will be repeated.

9.2.1.2 Handling of Specimens(s)

10 ml of blood should be collected in EDTA (Lavender) tube and centrifuged at 1600 RCF for 15 minutes. Plasma should transferred into two push cap tubes and can be stored at either -20 C or -80 C freezer.

9.2.1.3 Shipping of Specimen(s)

Specimens should be stored locally until study is closed to new patient entry. At that time, the specimens collected outside of M. D. Anderson should be shipped frozen on a Tuesday by overnight courier delivery to:

James C. Yao
University of Texas MD Anderson Cancer Center
FC 10.3000
1400 Holcombe Blvd
Houston, Texas 77030
Phone: 713-792-2828
Email: jyao@mdanderson.org

Please notify principle investigator by email prior to shipment.

9.2.1.4 Site(s) Performing Correlative Study

All participating sites.

9.3 Special Studies

9.3.1 Molecular testing

Patients from University of Texas M. D. Anderson Cancer center will be offered and approached for consent to participate on separate IRB-approved protocol "Molecular testing for the MD Anderson Cancer Center Personalized Cancer Therapy Program, PA11-0852".

Archival tumor specimens will be used among patients who consent to above study.

9.3.1.1 Mutational status using a targeted sequencing approach

9.3.1.2 Assessment

Relevant CLIA Testing will be done through the MD Anderson Molecular Diagnostics Laboratory (CLIA Cert #:45D0994328). First line testing will be done with the Actionable Cancer Gene Scan CLIA panel in the MD Anderson Molecular Diagnostic Laboratory. Currently this is an Ion Torrent Ampliseq-based hot-spot analysis of 46 genes. This includes following mutations: AKT1, PIK3CA, BRAF, KRAS, NRAS, GNAQ, GNAS, MET, IDH1/2, RET, ABL1, ALK, APC, ATM, CDH1, CDKN2A, CSF1R, CTNNB1, EGFR, ERBB2, ERBB4, FBXW7, FGFR1, FGFR2, FGFR3, FLT3, HNF1A, HRAS, JAK2, JAK3, KDR, KIT, MLH1, MPL, NOTCH1, NPM1, PDGFRA, PTEN, PTPN11, RB1, SMAD4, SMARCB1, SMO, SRC, STK11, TP53, VHL.

For patients with adequate DNA available, a portion of the DNA will be kept in the CLIA environment, and the test of the DNA will undergo research testing, T200 panel, a targeted whole exome sequencing assay, will be performed. CLIA confirmation of any positive research findings, if ordered, may be performed in the MDACC Diagnostic Laboratory. These studies are sponsored by the Institute of Personalized Cancer Therapy at M.D. Anderson Cancer Center.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. A standard window of -1 day to + 3 days will be considered acceptable for all testing, visits, and treatments (will not be considered study deviation).

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Off Study
Ziv-aflibercept		A			A			A			A			
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------X												
Physical exam	X	X			X			X			X			X
Vital signs	X	X			X			X			X			X
Height	X													
Weight	X	X			X			X			X			X
Performance status	X	X			X			X			X			X
CBC w/diff, plts, PT/PTT	X	X*			X			X			X			X
Serum chemistry[a]	X	X*			X			X			X			X
Urine protein creatinine ratio	X				X			X			X			
Adverse event evaluation		X----------X												X
Tumor measurements	X	Tumor measurements are repeated every *3 cycles*. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X
Radiologic evaluation for tumor assessment[f]	X	Radiologic measurements should be performed every 3 cycles (9 weeks)												X
B-HCG	X[c]													
Perfusion CT	X			X										X[d]
Blood VEGF-A, PlGF	X													
Optional consent for molecular testing on Clearinghouse protocol (PA11 - 0852)	X[e]													

A: Ziv-aflibercept: Dose as assigned; administration schedule
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Cross-sectional imaging (CT or MRI) of abdomen, pelvis, and any other sites of know disease should be performed.
c: Serum pregnancy test (women of childbearing potential).
d: Performed at time of document progression and patient is ≤ 28 days from last dose of Ziv-aflibercept. Patients who discontinue for reasons other than progression will not have this off study perfusion CT.
e: MD Anderson patients only
f: CT or MRI of abdomen, pelvis and any known site of active disease. CXR if no chest CT planned.
* Week 1 labs need not be repeated if pre-study labs were done within 10 days of cycle 1 day 1.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 3 cycles (9 weeks). In addition to a baseline scan, confirmatory scans should also be obtained 9 (not less than 4) weeks following initial documentation of objective response.

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

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with Ziv-aflibercept.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will only be considered measureable if there has been evidence of progression in those lesions.

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

the short axis will be measured and followed.

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

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

11.1.3 Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based

evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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

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

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

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

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

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

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

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

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

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

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

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

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

11.1.4.3 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 Duration of Response

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

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

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

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Data Reporting

12.1.1 Method

For phase 2 protocols: This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.

12.1.2 Responsibility for Data Submission

Study participants are responsible for submitting CDUS data and/or data forms to either the Coordinating Center or to the Lead Organization on the study quarterly. The date for submission to the Coordinating Center or to the Lead Organization will be set by them. CDUS does not accept data submissions from the participants on the study. When setting the dates, allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP by the quarterly deadlines (see Section 12.1.1). For trials monitored by CTMS, a quarterly report of data will be provided by Theradex to the

Coordinating Center.

Either the Coordinating Center or the Lead Organization is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.2 CTEP Multicenter Guidelines

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

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

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

12.3 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

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

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

   a. NCI will provide all Collaborators with prior written notice regarding the existence and

nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

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

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

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

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

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication,

manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints/Objectives

This is a single arm, open-label, phase II study of Ziv-aflibercept in patients with advanced pancreatic NET. The study endpoint is objective response rate according to RECIST 1.1. The primary objectives are to estimate the objective response rate of Ziv-aflibercept among patients with advanced pancreatic NETs and to test the hypotheses that baseline perfusion CT parameters can predict which patients with advanced pNETs will respond to treatment with Ziv-aflibercept.

13.2 Study Design/Sample Size/Accrual Rate

A sequential two-stage design will be used to estimate the response rate of Ziv-aflibercept in pNETs and test the hypothesis that baseline pCT can predict which patients with advanced pNETs will respond to treatment with Ziv-aflibercept.

In a recent phase III study of sunitinib versus placebo, treatment with VEGF TKI sunitinib was associated with significant improvement in PFS (11.4 (7.4–19.8) versus 5.5 (3.6–7.4) month; HR = 0.42 (0.26–0.66)) and objective response rate of 9% versus 0%. Given the inclusion of treatments who have received prior VEGF inhibitor therapy, a true response rate of 5% or less (H_0) would be considered uninteresting for further development. A true response rate of at least 20% (H_1) would be considered of interest for further investigation. These hypotheses are informed in part by the understanding that response rate will be expected to be somewhat lower among patients previously treated with VEGF inhibitors, despite the continued efficacy of serial VEGF inhibitor therapy, as demonstrated in the second-line pazopanib study in renal cell carcinoma, which estimated the response rate to be 19%(16), as compared with a 31% response rate in a randomized study of untreated renal cell carcinoma patients(30).

A two-stage design will be used to test whether there is sufficient evidence that the treatment could be a candidate for further study, with early stopping rules to terminate the study early for poor results.

Early stopping rules:
The following stopping rules will be applied hierarchically. Accrual will be held at time of interim analysis pending application of Stopping rule 1. Accrual will not be held for Stopping rule 2 or 3 at time of interim analysis, if random variation preclude adequate number of patients in subgroups at time of interim analysis.

Stopping rule 1: The first early stopping rule applies to all patients by applying the Simon's optimal two-stage design. In the first stage, we will enroll 21 evaluable patients. If 0 or 1 of the first 21 patients achieve RECIST response (PR or CR), the study will terminate. If at least 2 of the first 21 evaluable patients achieve RESCIST response (PR or CR), an additional 20 patients

will be enrolled. If at the end of the second stage, at least 5 out of 41 patients achieve RECIST response, the treatment will be considered acceptable for further testing. This design has a 4.6% chance of accepting the treatment for further testing if the true response rate is ≤ 5% (type 1 error = 0.046), and 85% power (type 2 error = 0.15) of accepting the treatment for further testing if the true response rate is at least 20%. The maximal accrual will be 41 evaluable patients. The probability of early termination is 72% under the null hypothesis.

Stopping rule 2: The second early stopping rule applies to the high perfusion CT subgroup. Analyses will be applied after completion of stage 1 of the minimax design and application of Stopping rule 1. Our target response rate in this putatively favorable subgroup (baseline BV > 5.25 and baseline PS > 25) is at least 30%. If the observed response rate is unlikely to reach 30% in this subgroup, the trial will be stopped early. The second early stopping rule will be evaluated after at least 9 evaluable patients are enrolled in the subgroup with both high BV (baseline BV > 5.25) and high PS (baseline PS > 25). If there is no responder in both the high BV and the high PS subgroup when at least 9 evaluable patients are enrolled, the trial will be stopped early. Otherwise, that is, if at least one response is observed in this subgroup, the trial will continue. This stopping rule will have at least 96% power if the response rate is 30% of higher in this favorable subgroup.

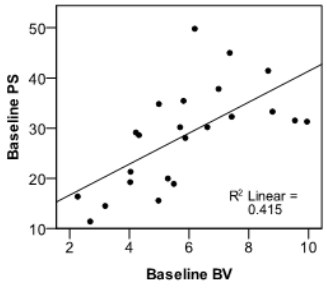
When both the first and second stopping rules are considered together, the trial will be stopped early when either of the rules reaches the stopping boundaries. As a result, the trial will be stopped early when either the response rate is low in the overall group or in the favorable subgroup.

Stopping rule 3: The third early stopping rule applies to the low perfusion CT subgroups. Analysis will be applied after completion of stage 1 of the minimax design and application of Stopping rules 1 and 2 if there are at least 18 patients in the low BV subgroup or the low PS group. The goal of the stopping rule is to stop enrollment of patients to the putative unfavorable group if patients in the group are unlikely to benefit from therapy. Based on the historical sunitinib phase 3 study, the response rate to sunitinib is 9% (90% CI, 5% – 16%). If no responders are observed among at least 18 evaluable patients, we can rule out a response rate of 16% or higher with 95% power and the subgroup would terminate.

At the end of the study, 90% exact confidence interval will be constructed for the overall group and for all the marker subgroups respectively. In addition, we will test **the hypothesis that baseline perfusion CT parameters can predict which patients with advanced pNETs will respond to treatment with Ziv-aflibercept.** All enrolled patients will have baseline perfusion CT. Threshold for baseline BV (5.25 ml/100gram) and PS (25 ml/minute/100gram) were established from prior studies of VEGF inhibitors among patients with pancreatic NET treated at M. D. Anderson. Approximately 60% of pancreatic NET had baseline BV > 5.25 and approximately 60% had baseline PS > 25. The following RECIST response rates were observed by baseline measurements.

Baseline BV		Baseline PS	
BV < 5.25	BV > 5.25	PS < 25	PS > 25

0%	57%	12.5%	46.7%



One goal of the proposed study is to test the NULL hypothesis that the proportion of RECIST response is identical in the two populations (those above and below the pCT parameter threshold). We are testing 2 separate hypotheses (BV and PS). However, BV and PS are highly correlated (Pearson, P<.0001). Furthermore, considering that this study is a phase II trial, we do not adjust the significance level (alpha) for the proposed two tests. Due to the limited sample size, Fisher's exact test will be applied to test the equal response rates between the two groups with a one-sided 5% type I error rate. The one-tail test means that only an effect in the expected direction will be interpreted.

Alternate hypotheses:

- Pancreatic NETs with baseline BV > 5.25 will have a higher response rate than those with BV ≤ 5.25.

  Assuming a similar distribution of patients in terms of baseline BV, 25 patients will have BV > 5.25 and 16 patients will have BV ≤ 5.25. The study will have power of 86% to yield a statistically significant result. This computation assumes that the difference in proportions is 0.40 (specifically, 0.45 versus 0.05). Power calculations for alternate distribution of baseline BV are included in table below.

RR (BV>5.25)	RR (BV≤5.25)	N (BV>5.25)	N (BV≤5.25)	Power
0.45	0.05	11	30	.79
0.45	0.05	16	25	.86
0.45	0.05	21	20	.88
0.45	0.05	25	16	.86
0.45	0.05	30	11	.78

- Pancreatic NETs with baseline PS > 25 will have a higher response rate than those with BV ≤ 25.

  Assuming a similar distribution of patients in terms of baseline PS, 25 patients will have PS > 25 and 16 patients will have PS ≤ 25. The study will have power of 67% to yield a statistically significant result. This computation assumes that the difference in proportions is 0.35 (specifically, 0.47 versus 0.12). Power calculations for alternate distribution of baseline BV are included in table below.

RR (PS>25)	RR (PS≤25)	N (PS>25)	N (PS≤25)	Power
0.47	0.12	11	30	.62
0.47	0.12	16	25	.69
0.47	0.12	21	20	.70
0.47	0.12	25	16	.67
0.47	0.12	30	11	.59

The planned sample size is 41 patients. The expected accrual rate is approximately 3 patients per months.

The following accrual targets for gender, race, and ethnicity are based on analyses of 371 patients with pancreatic NETs seen at University of Texas M. D. Anderson Cancer Center. By gender 47% were female; 53% were male. By ethnicity, 8% were Hispanic or Latino. By race, 3% were Asian; 8% were black; 88% were white.

Accrual Targets								
Ethnic Category	**Sex/Gender**							
	Females			**Males**			**Total**	
Hispanic or Latino	1		+	2		=	3	
Not Hispanic or Latino	18		+	20		=	38	
Ethnic Category: Total of all subjects	19	(A1)	+	22	(B1)	=	41	(C1)
Racial Category								
American Indian or Alaskan Native	0		+	0		=	0	
Asian	0		+	1		=	1	
Black or African American	1		+	2		=	3	
Native Hawaiian or other Pacific Islander	0		+	0		=	0	
White	18		+	19		=	38	
Racial Category: Total of all subjects	19	(A2)	+	22	(B2)	=	41	(C2)
	(A1 = A2)			(B1 = B2)			(C1 = C2)	

13.3 Analysis of Secondary and Exploratory Endpoints

Due to the phase II nature of this study and the high correlation between the two pCT endpoints, no formal adjustment will be made for multiple analyses of secondary and exploratory study objectives.

Analysis plan for secondary study objectives:

- Estimate progression free survival (PFS) duration among patients treated with ziv-aflibercept.
  PFS will be calculated from the date of study registration for all eligible patients using the Kaplan Meier method and reported with confidence interval.

- Evaluate the relationship between response rate and baseline BV and between response rate and baseline PS.
  In addition to hypothesis testing using externally generated cut-points, refinement of optimal cut points in baseline BV and baseline PS separating responders and non-responders will be performed.
  - Receiver operating characteristic (ROC) curves will be generated for both parameters.

- Response rates of pCT subgroups defined by these cut-points will be compared using chi-square test.
- Response profiles of pCT subgroups defined by these cut-points will be compared using non-parametric test (Wilcoxon rank sum test).

Analysis plan for exploratory study objectives:

- Determine whether post-treatment changes in BV expressed as relative change from baseline correlate with response to ziv-aflibercept.
    - Median will be used as cut point for correlation of post-treatment changes in BV expressed as relative change from baseline with response.
    - Response rates will be compared using chi-square test or Fisher's exact test whenever appropriate.
    - Response profiles will be compared using non-parametric test (Wilcoxon rank sum test).

- Determine whether post-treatment tumor blood flow (BF) (absolute measurement) correlates with response to ziv-aflibercept
    - Median will be used as cut point for correlation of post-treatment tumor blood flow (BF) (absolute measurement) with response.
    - Response rates will be compared using chi-square test or Fisher's exact test whenever appropriate.
    - Response rates will be compared using chi-square test or Fisher's exact test whenever appropriate.

- Determine whether post-treatment changes in BF and, BV, expressed as relative change from baseline, correlate with relative change in sum of tumor diameters (RECIST 1.1 measurements)
    - Continuous parameters in relative change in pCT parameters will be plotted against best relative change in sum of tumor diameters from RECIST 1.1 tumor measurements.
    - Pearson correlation will be used to test statistical significance. Non-parametric test will be used if appropriate.

- Determine the effect of ziv-aflibercept therapy on post-treatment blood flow (BF), BV, mean transit time (MTT), and PS at 4 weeks after treatment
    - Descriptive statistics of pre and post treatment values will be given.
    - Distribution of pre and post treatment values will be graphed
    - Treatment induced change in values will be compared using paired-t test. Non-parametric test will be used if appropriate.

- Evaluate the changes in tumor perfusion parameters at time of progression
    - Summary statistics will be given to describe change from baseline and change from post treatment pCT.
    - Differences will be compared using paired-t test. Non-parametric test will be used if appropriate.

13.4 For phase 2 protocols only: **Reporting and Exclusions**

13.4.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with Ziv-aflibercept.

13.4.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B CTEP MULTICENTER GUIDELINES

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

Responsibility of the Protocol Chair

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

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

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

Agent Ordering

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

APPENDIX C NEW YORK HEART ASSOCIATION CLASSIFICATION OF FUNCTIONAL CARDIAC CAPACITY

Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

*The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

APPENDIX D REGISTRATION FORM

Registration Form

Date: _____

Registration Site _____ Site Number _____

Date subject signed consent _____

Subject Initials _____ Date of Birth (Mo/Day/Year) _____

Subject number _____

Enrolling Investigator _____

Research Nurse _____

Telephone _____

Fax Number _____

Email address _____

Data Coordinator _____

Telephone _____

Fax Number _____

Email address _____

Met	Not met	INCLUSION
		Patients must have histologically or cytologically confirmed low or intermediate grade pancreatic NET. Patients with neuroendocrine tumors associated with MEN1 syndrome will be eligible.
		Patients must have unresectable or metastatic disease.
		Patients must have at least one measurable site of disease according to RECIST 1.1 that has not been previously irradiated.
		Patients must have at least one lesion suitable for perfusion CT. The lesion should be greater than or equal to 3 cm in size in the cranial caudal direction.
		Patient must have no contraindication for CT with iodinated contrast
		Patients who are on a somatostatin analogue for control of hormonal syndromes must be on a stable dose (no change in mg dose of long acting octreotide or lanreotide, changes in dosing interval of +/- 1 week is allowed) for 2 months prior to date of study entry.
		Women of child-bearing potential must have a negative serum pregnancy test within 7 days prior to date of study entry. Women who have had menses within the past 2 years, who have not had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy are considered to be of child-bearing potential. Patients with elevated hCG at baseline that is judged to be related to the tumor are eligible if hCG levels do not show the expected doubling when repeated 5-7 days later, or pregnancy has been ruled out by vaginal ultrasound.
		Any number of prior lines of systemic anti-neoplastic therapy are allowed. For purpose of this criterion, somatostatin analogues will not be counted toward lines of systemic anti-neoplastic therapy and only one prior VEGF inhibitor will be allowed.
		Patients must have normal organ and marrow function as defined below:
		leukocytes ≥3,000/mcL
		absolute neutrophil count ≥1,500/mcL
		platelets ≥100,000/mcL
		total bilirubin ≤1.5 × institutional upper limit of normal
		AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal
		creatinine within normal institutional limits
		creatinine clearance ≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.
		Urine protein:creatinine ratio ≤ 1.0.
		OR
		24-hour urine protein ≤ 1000 mg (24-hour total urine protein only need be obtained if urine protein : creatinine ratio < 1.0)
		Patients must have PT/INR/PTT within 1.2 X the upper limit of normal.
		Patients must have resting blood pressure (BP) no greater than 140 mmHg (systolic) or 90 mmHg (diastolic) for eligibility. Initiation or adjustment of BP medication is permitted prior to study entry.
		Ability to understand and the willingness to sign a written informed

		consent document.
Met	**Not met**	**EXCLUSION**
		Less than 28 days elapsed from prior radiotherapy, from prior surgery and prior chemotherapy to the time of randomization. Less than 42 days elapsed from prior major surgery to the time of randomization.
		Adverse events (with exception of alopecia, peripheral sensory neuropathy and those listed in specific exclusion criteria) from any prior anti cancer therapy of grade >1 (National Cancer Institute Common terminology Criteria [NCI CTCAE] v.4.0).
		Age < 18 years
		ECOG PS > 2
		History of brain metastases, uncontrolled spinal cord compression, or carcinomatous meningitis or new evidence of brain or leptomeningeal disease.
		Other prior malignancy. Adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix or any other cancer from which the patient has been disease free for > 5 years are allowed.
		Participation in another clinical trial and any concurrent treatment with any investigational drug within 30 days prior to randomization.
		Any of the following within 6 months prior to randomization: myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, NYHA class III or IV congestive heart failure, stroke or transient ischemic attack.
		Any of the following within 3 months prior to randomization: Grade 3-4 gastrointestinal bleeding/hemorrhage, treatment resistant peptic ulcer disease, erosive oesophagitis or gastritis, infecttious or inflammatory bowel disease, diverticulitis, pulmonary embolism or other uncontrolled thromboembolic event.
		Occurrence of deep vein thrombosis within 4 weeks, prior to randomization.
		Acquired immuno deficiency syndrome (AIDS-related illnesses) or known HIV disease requiring antiretroviral treatment.
		Any severe acute or chronic medical condition, which could impair the ability of the patient to participate to the study or to interfere with interpretation of study results.
		Pregnant or breast feeding women. Positive pregnancy test (serum or urine β-HCG) for women of reproductive potential.
		Patient with reproductive potential (female and male) who do not agree to use an accepted effective method of contraception (hormonal or barrier methods, abstinence) during the study treatment period and for at least 3 months following completion of study treatment. For female patient enrolled, the following methods of contraception are acceptable: oral contraceptives accompanied by the use of a second method of contraception, as it is not known how oral contraceptives interact with all study medications or Intra Uterine Device (IUD) or women who are surgically sterile, or women who are post –menopausal or other reasons have no chance of becoming pregnant.
		Absence of signed and dated Institutional Review Board-approved patient informed consent from prior to enrollment in the study.
		Exclusion criteria related to ziv-aflibercept:

		Urine protein-creatinine ratio (UPCR) >1 urinalysis or total urine protein > 500 mg/24h.
		Serum creatinine > 1.5 x upper limit of normal (ULN). If creatinine 1.0-1.5 x ULN, creatinine clearance, calculated according to Cockroft-Gault formula, < 60 ml/min will exclude the patient.
		History of uncontrolled hypertension, defined as blood pressure > 150/100 mmHg (grade ≥2 according to NCI CTCAE v. 3.0), or systolic blood pressure >180 mmHg when diastolic blood pressure < 90 mmHg, on at least 2 repeated determinations on separate days within 3 months prior to study enrollment.
		Patients on anticoagulant therapy with unstable dose of warfarin and/or having an out-of- therapeutic range INR (>3) within the 4 weeks prior to study entry.
		Evidence of clinically significant bleeding diathesis or underlying coagulopathy (e.g. INR>1.5 without vitamin K antagonist therapy), non-healing wound.

APPENDIX E NCISS MULTICENTER STUDY MANAGEMENT PLAN

Multi-Center Study Management Plan

For

National Cancer Institute (NCI) / Cancer Therapy Evaluation Program (CTEP) Phase I/II & Phase II Studies

Version 4/10

Table of Contents

1.0 INTRODUCTION

This Study Management Plan (SMP) outlines the procedures and requirements for institutions collaborating with MD Anderson Cancer Center (MDACC) in the conduct of a National Cancer Institute (NCI)/Cancer Therapy Evaluation Program (CTEP) sponsored research protocol.

2.0 PURPOSE

To establish standards that will ensure compliance with Federal Regulations, Good Clinical Practice (GCP) Guidelines; and Health Insurance Portability and Accountability Act (HIPAA) requirements in accordance with the CTEP Multicenter Guidelines.

3.0 GENERAL ROLES AND RESPONSIBILITIES

In accordance with the CTEP Multicenter Guidelines, the MDACC Principal Investigator, MDACC NCI Support Services (MDACC NCISS), and the participating institution will all agree to the general responsibilities as follows (specific procedures for these general responsibilities are detailed in the SMP):

3.1 MDACC Principal Investigator (MDACC PI)

The MDACC PI will accept responsibility for all aspects of the Study Management Plan to include:

Protocol Development

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments by the NCI and the MDACC IRB.
- List each participating investigator and institution on the protocol title page including address, phone number, and email and designate the lead institution on the title page.
- Assure all participating institutions are using the correct version of the protocol.

Study Oversight

- Monitor progress and overall conduct of study at all participating institutions.
- Ensure all CTEP reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- **Research Team Teleconferences:** The MDACC PI & research team, MDACC NCISS, and participating institution PI and research staff will participate in a

teleconference every 2 – 4 weeks, as needed, and will discuss the following information

- Patients enrolled at participating sites including
  - Brief history
  - Eligibility for trial
  - Status of treatment
  - Adverse Events
  - Response evaluation

- Review of safety data
  - Unexpected toxicities
  - Serious Adverse Events
  - IND safety reports

3.2 MDACC NCI Support Services (MDACC NCISS)

To assist the MDACC PI in meeting his/her responsibilities MDACC NCISS will assume the following general responsibilities:

Administrative Support

- Act as the central liaison between the MDACC PI, participating institution, and NCI CTEP/PIO Office.

- Maintain a contact list of all study participants at MDACC and the participating institution.

Regulatory Management

- Distribute approved protocols to participating institutions, notify them of amendments, and provide them with copies of approved amended protocols.

- Ensure that each participating institution has the appropriate assurance on file with the Office of Human Research Protection (OHRP form 310) and this has been submitted to the CTEP PIO.

Regulatory Document Collection: Refer to Section 3.3 (page 70) for a list of documents that must be submitted to MDACC NCISS prior to protocol activation and submitted on an ongoing basis for the duration of the study.

Study Management Support

- Conduct study initiation meetings with MDACC PI and provide support to the participating institution research staff, as required.

- Distribute external Serious Adverse Event safety reports to participating sites.

- Notify participating institutions of protocol hold or closure.

Data Management Support

- Provide participating sites with access, training, and support for electronic data entry.
- Notify participating institution research teams of data locks prior to quarterly data transmission due dates
- Monitor data quality and issue data queries / error log findings.

Quality Assurance

- Coordinate and participate in regularly scheduled teleconferences with the MDACC PI, the participating institution PI and their respective research teams to review study conduct.
- Audit participating institutions by on-site inspection of selected patient records and / or by requesting source documents and research records as requested.

3.3 Participating Institution Principal Investigator

The general responsibilities for each participating institution are as follows:

Regulatory Compliance

- **Study Contact List:** Provide a list of key study personnel and update MDACC NCISS with research staff changes on a timely basis.
- **NCI Investigator Registration:** Maintain an active NCI Investigator Registration number for any physician who will be consenting / treating patients to the study and provide confirmation of annual renewal.
- **IRB Approval**: Submit protocol and amendments to local IRB prior to initiating any protocol activity / changes.

  Note: If IRB approval for amendments is not obtained within the timeframe specified at time of amendment distribution accrual will be suspended until IRB approval is obtained.
- **Regulatory Documents:** Provide copy of required regulatory documents to MDACC NCISS prior to activation.

  1. Federal Wide Assurance (FWA) number
  2. Laboratory certifications (CLIA / CAP)
  3. Normal laboratory values
  4. NCI Investigator Registration Number/expiration dates for all physicians
  5. Delegation of authority log
  6. Copy of initial IRB approval documents

The following regulatory documents must be submitted on an ongoing basis for the duration of the study:

1. Copy of IRB annual approval documents. Note: If IRB annual approval is not received prior to the anniversary of the previous approval, accrual will be suspended until the annual approval is received.
2. Copy of IRB approval documents for any protocol or informed consent revisions. Note: If IRB approvals for amendments are not received within the timeframe indicated at the time of distribution, accrual will be suspended until IRB approval is obtained.
3. Confirmation of renewal of NCI Investigator Registration Number
4. Copy of CTEP-AERS reports for Serious Adverse Events
5. Evidence of IRB review of external safety reports
6. Protocol violations and deviations submitted to the participating institution IRB.
7. Copy of all signed informed consents for patients enrolled on the trial, if requested by the MDACC PI.
8. Copy of IRB approval documents for any protocol status changes: activation, study closed to new patient enrollment, study closure, study termination. Note: If IRB annual review is not provided on or before the anniversary of the previous approval, accrual will be suspended until the annual re-approval is received.

- **IND Safety Reports:** MDACC NCISS will distribute IND safety reports and appropriate guidance regarding IRB submissions and patient notification to the participating institutions.

Study Management

- **Eligibility:** Ensure patients meet all eligibility criteria prior to registering the patient on study.

- **Adverse Events:** Submit Expedited Adverse Event reports directly to CTEP (via CTEP-AERS) as required per protocol and provide copies to the MDACC PI and NCISS. Submit Routine Adverse Events via Clinical Oncology Research System (CORe.)

- **Protocol Compliance:** Adhere to the MDACC IRB definition of protocol deviation and protocol violation and requirements for reporting.

  Protocol Deviation: Noncompliance with the protocol that does not have a significant effect on the subject's rights, safety, welfare, and/or the integrity of the data. Deviations may be caused by the action of the subject, the investigator, the research staff, or natural events.

Protocol Violation: Changes to protocol procedures without prior approval of the IRB/Sponsor. These changes may have a significant effect on the subject's rights, safety, welfare, and/or the integrity of the data, and may cause an unanticipated problem to the subject or others. Violations may also significantly alter the clinical effectiveness of the treatment or the evaluation of its toxicity.

Procedures for Reporting Protocol Violations/Deviations

Participating Institutions: Protocol violations/deviations occurring at a participating institution will be submitted to that site's own IRB. A copy of the participating institution's IRB violation/deviation report will be forwarded to the MDACC NCISS **within 7 calendar days after the original submission.**

Coordinating Center: Upon receipt of the violation/deviation report from the participating institution, MDACC NCISS will submit the report to the MDACC PI for review.

Data Collection

The Clinical Oncology Research System (CORe) is a web based database that is used for patient registration (for Phase I, Phase I/II and Phase II trials) and data entry (for Phase I/II, II trials). CORe can be accessed at www.oncologyresearch.org . Study staff at participating institutions will be provided with a username and password for CORe at the time of study activation.

- **Patient Registration:** All patients, regardless of the phase of the trial, will be registered in CORe prior to beginning treatment.

  *At the time of registration portions of a patient's protected health information will need to be entered. In order for the site to enter this information the patient must have signed an informed consent document, which includes an authorization for the release of protected personal health information (IC/A). The authorization that each institution obtains to use and disclose protected health information **must** include MD Anderson Cancer Center as an entity that they will share data with. This consent and authorization (IC/A) document authorizes MD Anderson Cancer Center to collect and retain documents, reports, and/or information which relate to the patient's participation on the protocol. This document also authorizes MD Anderson Cancer Center to send data and/or composite data for the entire study to each site participating in the trial.*

- **Data Entry:** Enter data in CORe according to the following data schedule

At time of registration (Phase I/II and II trials)	• Assign patient number • Name & demographics

	• Eligibility checklist
Within 1 week of registration (Phase I/II and II trials)	• Pre-study data including o Registering institution o Disease subgroup code (NCI CDU) o Disease code (NCI CDU) o Payment method (NCI) o Zubrods PS o Baseline abnormalities o Prior therapy o Number of prior chemo regimens
Within 3 weeks after the completion of each cycle. (Phase I/II and II trials)	• Treatment Course o Course Number o Cycle start date o Treatment code (NCI CDU) o Height (cm) o Weight (kg) o AE Experienced o Treating institution • Treatment Agent o Agent code (NCI CDU) o Total dose this course o Dose change • Adverse Events o Adverse event o Symptoms (required if AE other used) o Grade o Onset date o Resolved date o Relationship o AE report sent to CTEP
Within 1 week after the completion of the cycle required for response assessment (Phase I/II and II trials)	• Protocol Summary o Last dose date (date of last treatment) o Off treatment reason (if applicable) o Evaluability o Evaluable for response o Protocol response o Response date o Progression date (if applicable)
Within 1 week after completing treatment or taken off study (Phase, I/II and II trials)	• Off Protocol o Off date o Death date (if applicable) o Death date source o Death comment o Cause of death

Specifics Regarding Phase II Trials

- **Data Locks:** Data will be transmitted to NCI quarterly on January 31, April 30, July 31, and October 31. ***Approximately 3 weeks prior to the transmission date, the participating institution will be informed by MDACC NCISS that the data will be locked during data transmissions. During this period of data lock, no new patient data and/or changes to previously entered data should be made unless instructed by MDACC NCISS.***

- **Data Queries:** Following data transmission NCI will issue an error log to MDACC NCISS detailing any corrections that need to be made to data prior to protocol acceptance. MDACC NCISS will communicate the required changes to the participating institution. NCISS will periodically review the data for completeness. You may receive queries directly from NCISS prior to data submission to the NCI. ***Required data corrections must be completed as instructed by MDACC NCISS.***

4.0 PATIENT CONFIDENTIALITY AND AUTHORIZATION STATEMENT

The Health Insurance Portability and Accountability Act of 1996 contains, as one of its six major components, the requirement to create privacy standards for health care information that is used or ***disclosed in the course of treatment, payment or health care operations.*** The original Privacy Rule, as it has come to be known, was published in December 2000. The Final Rule was published on August 14, 2002, which has modified the privacy rule in significant ways vis-à-vis research.

In order for covered entities to use or disclose protected health information during the course of an MDACC Multicenter trial the participant in the trial must sign an authorization form. This Authorization may or may not be separate from the Informed Consent. The Authorization may require local IRB approval before presentation to a potential trial participant. The participating institution, with the approval from the NCI/CTEP and MDACC, will provide an Informed Consent template, which covered entities, must use.

MDACC and participating institutions will attempt to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected per National Cancer Institute requirements. These are the primary reasons why MDACC has chosen to use Authorizations, signed by the participant on the trial, rather than limited data sets with data use agreements.

5.0 ON-SITE AUDITING

Purpose of Audit

To ensure that the data analyzed to determine study results accurately reflect the primary source documents and that any clinical study was conducted in accordance with an Institutional Review Board (IRB)-approved protocol. The audit program reviews protocol management in the following categories: eligibility, informed consent, treatment, disease

outcome/response, toxicity, and general data quality. Compliance with all federal, National Cancer Institute and institutional requirements for the protection of human subjects is also assessed.

In addition, the audit program provides education to the research staff regarding issues identified during the audit and assists research teams to develop appropriate ways to correct deficiencies identified by the audit.

Selection for Audit

Participating institutions can be selected for audit at any time. Audit will generally be performed on a random basis and may occur at 6 – 12 month intervals.

Audit Notification

The participating institution principal investigator (PI) and study coordinator shall be notified two to four weeks in advance of the audit start date. If the audit is initiated due to suspected deficiencies the advance notice may be shorter than 2 weeks. All audit notifications shall be delivered to the PI and study coordinator by e-mail. It is important that a person who is familiar with the research protocol and the study subjects enrolled on the trial be available (but not necessarily present) during the audit to assist the auditors in locating documentation that may be difficult to find in the primary medical record.

The notification will include:

- The date of the audit
- A list of the patient records to be audited
- A list of documents required for the audit

Responsibilities of Participants in the Audit

Clinical Trials Auditors: If more than one auditor visits the site a lead auditor will be designated to guide the audit process. It shall be the auditor's responsibility to print a copy of the protocol and be familiar with the study prior to the start of the audit.

Principal Investigator and Research Staff: The principal investigator is responsible for assuring that all requested audit materials are available at the time of the audit. These materials shall include the following:

- One copy of an original signed and dated informed consent document (ICD) for each participant. For patients who have been re-consented while on study, an original signed and dated informed consent must be available for each IRB-approved version of the informed consent.

- All patient records: in-patient charts (if applicable), protocol-specific patient source documents (signed and dated pill diaries, symptom records), database printouts, and patient research files
- Correspondence and source documentation from outside institutions pertaining to patient research data
- Radiology films and other specified studies, if requested
- Any operative, pathology and radiotherapy reports required by protocol
- Regulatory Binder

The research staff must have all patient research charts and the Regulatory Binder organized in a systematic and consistent fashion. The presence of organized study records reduces the potential for queries and helps prevent repeated questions to the study coordinator / PI requesting assistance in locating items during the audit.

Conducting the Audit

Medical Record Review: At the time of the medical record audit, source documentation shall be reviewed and used to independently verify study data. Data quality shall be assessed by measuring it against the standards for optimal data collection as defined in the research protocol. Data entered in CORE should match precisely with the corresponding information on the primary source document.

The research team shall also be evaluated on protocol compliance with the study schedule, regulatory requirements, and guidelines for Good Clinical Practice (GCP). Although the PI may delegate responsibilities for various aspects of the protocol management, the PI alone retains ultimate responsibility for the conduct of the clinical trial.

The following elements are reviewed during the audit:

Activation/Continuing Review Information: The auditor shall verify that:

- IRB approval has been obtained prior to study activation and patient enrollment;
- An annual continuing review has been completed within 365 days from initial date of approval;
- Confirmation that all consenting physicians have a current NCI Investigator Registration number
- Protocol amendment, informed consent, and IRB approval dates are appropriate;
- Patients were treated following CORe registration.
- All regulatory documents are in the regulatory binder(s)

Informed Consent Document: The ICD must:

- Be the appropriate IRB-approved version at the time the patient was enrolled. For NCI studies, the ICD must also have received NCI's approval before it is used in obtaining informed consent.
- Contain the patient's signature and date;
- Contain the signature and date of the person who is obtaining the informed consent;

- Contain the signature of the witness and date it was signed; if applicable
- Indicate selection of optional studies verified by patient initials
- List M. D. Anderson as an authorized reviewer on ICD's from outside institutions (where M. D. Anderson serves as the lead institution on a multicenter trial). On multicenter trials where M. D. Anderson is not the lead site, any institution that may request protected health information should be listed in the HIPAA section of the M. D. Anderson ICD.

The informed consent process must be documented in the on-study note located in each patient's medical record.

Eligibility: The eligibility checklist is compared against the primary medical record to confirm that all criteria were met prior to registration on the trial. If documentation cannot be located, eligibility is noted as "unable to confirm" due to insufficient data. The patient shall be considered ineligible if one or more of the eligibility requirements were not satisfied.

Protocol Compliance: Source documentation is used to verify that the performance status has been assessed and that the results of all required tests have been obtained within the protocol-specified time frame prior to the start of treatment. On-study visits, lab tests, and diagnostic studies shall be checked for adherence to the study schedule. If testing or visits were missed, the auditor shall verify that a protocol deviation/violation report was completed for each occurrence and submitted to the IRB, and a copy placed in the Regulatory Binder. A deviation log may be utilized as per institutional policy.

Treatment Administration: The audit team confirms that patients receive the correct dose, route, dosing interval, and timing of the treatment administered. Dose modifications shall also be checked and compared against the protocol. The auditor shall assure that the proper body surface area (BSA) was calculated. The auditor shall also check the medical record for correct and consistent recording of the study subject's weight and shall look for dose adjustments based on body weight changes as defined in the protocol.

Disease Outcome / Response: The auditor shall verify baseline and on-study disease status by reviewing tumor measurements analyses in the medical record/research file. Solid tumor measurements shall be compared to imaging reports and/or original radiology films to confirm tumor response. For hematologic tumors, documented response shall be verified using appropriate analyses as stated in the protocol. If the auditor cannot verify the outcome response, a physician auditor shall be consulted for a final decision.

Toxicity: All toxicities shall be documented in the medical record or recorded on patient data forms. These shall include the appropriate Common Toxicity Criteria term to describe the toxicity, the grade of toxicity, the attribution, date of onset, and date of resolution. The auditor shall confirm that all patients have been followed for toxicities for thirty days from the last date of protocol therapy. When a SAE occurs, the auditor shall verify that initial and follow-up reporting is appropriate as required in the Code of Federal Regulations and in accordance to NCI / CTEP's policy.

General Data Quality: This category concerns the quality and completeness of source documentation as well as the accuracy of data transcription from the source document to the case report form. Emphasis shall be placed on clear and complete reporting of the findings and correct matching of all data elements. Any inconsistent, incomplete, illegible, or hard to follow records shall be noted. Comments shall be made regarding repeated discrepancies that appear to affect the validity of the data or indicate that the management of the protocol needs more oversight.

Audit Findings

- Following completion of the audit, a preliminary audit findings report will be completed and be presented at the Audit Findings meeting or the "Exit Interview meeting".
- The purpose of the exit interview is to provide an opportunity for education, clarification, immediate dialogue, and feedback. It is not intended as a time to resolve all of the issues noted in the audit findings.
- The principal investigator and the study coordinator responsible for the study being audited are required to attend. Additional research staff associated with the study is encouraged to attend as well.
- As time allows, the lead auditor shall educate the research team in interpretation of the various regulatory requirements / institutional policies and shall provide guidance on the development of a corrective action plan to address issues involving major deficiencies.
- At the conclusion of the exit interview, the lead auditor may also discuss best practice guidelines and offer suggestions for improvement on data collection and protocol management.
- Following the exit interview the lead auditor shall amend the audit findings to include any corrections/clarifications noted during the exit interview.
- Once the audit findings have been modified, the lead auditor shall send a return receipt e-mail containing a copy of the audit findings to the PI and study coordinator.
- Upon receipt of the e-mail, the research team shall have two weeks to respond and return the audit findings to the lead auditor.
- The PI/study coordinator shall be responsible for providing a written response to each of the findings cited during the audit.
- To properly respond to the audit findings, the research team must enter a response immediately below each query. All research team responses shall be entered in red directly onto the audit findings document.
- When appropriate, a corrective action plan shall be included to complete the response.
- In situations where the lead auditor must review a source document to verify a research team response, the study coordinator shall provide a photocopy of this source document. All photocopies must be provided to the lead auditor by the deadline for audit response noted in the e-mail.
- Once all of the queries have been addressed and the response is complete, both the individual preparing the document and the PI for the study must print out and sign one copy of the audit findings report. An electronic copy of the same document shall be e-mailed to the lead auditor.

- Once the lead auditor receives the electronic copy of the response to the audit findings, he or she shall review the explanations/corrective action plans and shall create a summary report of outstanding audit findings, PI responses and any other audit activities.
- The final audit report will be forwarded to the Lead PI, the MD Anderson IRB.