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Brief Title: Ziv-Aflibercept for Advanced Progressive Carcinoid Tumors

Full Title: **Phase II Study of Ziv-aflibercept in Patients with Advanced, Progressive Carcinoid Tumors**

Phase II Study of Ziv-aflibercept in Patients with Advanced, Progressive Carcinoid Tumors.

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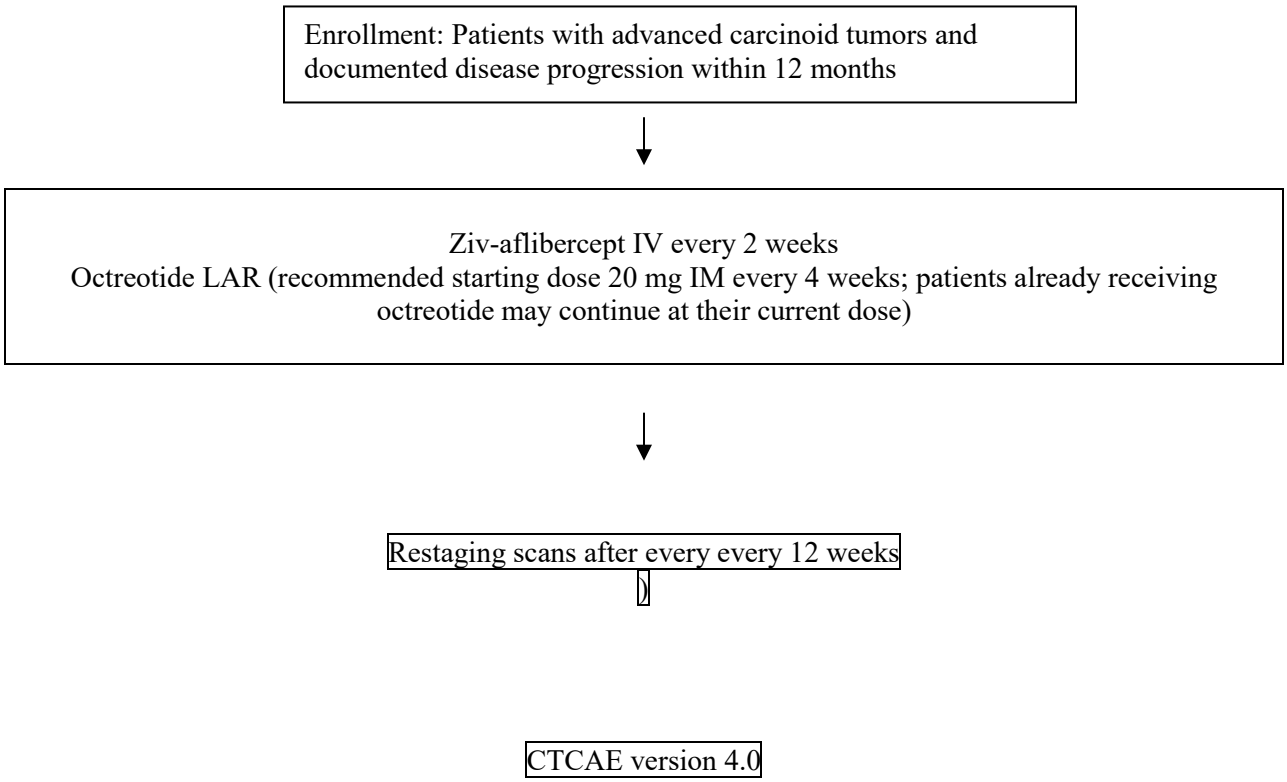

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1. OBJECTIVES:

The overall objective of this Phase II study is to assess the potential antitumor activity of Ziv-aflibercept in patients with advanced, progressive carcinoid tumors.

1.1 Study Design

This is a single arm, Phase II trial with estimated sample size of 43 patients. Patients with progressive, metastatic carcinoid tumors will receive Ziv-aflibercept (VEGF Trap) administered intravenously every two weeks. All patients will concurrently receive octreotide. Patients will be followed for evidence of toxicity and response, with imaging studies performed every 12 weeks.

1.2 Primary Objective

- To evaluate the progression-free survival (PFS) duration of patients with metastatic, unresectable, progressive carcinoid tumors treated with Ziv-aflibercept.

1.3 Secondary Objectives

- To determine the safety and tolerability of Ziv-aflibercept in patients with advanced carcinoid tumors
- To evaluate disease response (Partial Response [PR], Complete Response [CR], Stable disease [SD]), using RECIST criteria, version 1.1 of patients with advanced carcinoid tumors treated with Ziv-aflibercept
- To evaluate biochemical response, using levels of chromogranin-A and urinary 5-HIAA measured at baseline and following treatment with Ziv-aflibercept

2. BACKGROUND

2.1 Study Agent: Ziv-aflibercept

Ziv-aflibercept is also referred to as "VEGF Trap". 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 drug product is formulated as a sterile liquid for intravenous administration.

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.

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.

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]).

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 (69 to 226 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.

The toxicity profile of Ziv-aflibercept was evaluated in monkeys. The main compound-related microscopic findings were in the bone, nasal cavity, kidney, ovary, and adrenal gland. In the bone, Ziv-aflibercept-induced effects consisted mainly of thickening of the growth plate and osteocartilaginous exostoses observed on the axial and appendicular skeleton that correlated with hunched posture at clinical examination. In the nasal cavities, degeneration/regeneration of the respiratory and olfactory epithelium, and atrophy/loss of nasal septum and/or turbinates was often associated with hemorrhage and suppurative exudate. Histopathologic findings in the kidneys (increased glomerular mesangial matrix) were associated in a few animals with decreased serum total protein and albumin levels and increased serum blood urea nitrogen (BUN) and urine protein and/or microalbumin levels. In the ovaries, the decreased number of maturing follicles, granulose cells, and/or theca cells was associated with an overall inhibition of the female reproductive function. In the adrenals, a decreased vacuolation of adrenal zona fasciculata cells with cytoplasmic eosinophilia was observed. In addition, focal vascular proliferation/degeneration was noted in a range of organs, including in particular the digestive system, urinary bladder, heart, and brain of a few monkeys. In addition, increased liver enzyme levels were noted in a few monkeys with portal inflammation and necrosis. Ziv-aflibercept administration also resulted in a decrease in sperm motility and increased incidence of abnormal spermatozoa morphology. Most Ziv-aflibercept-related findings were noted from the lowest doses tested (1.5 to 3 mg/kg/administration). With the exception of osteocartilaginous exostoses and nasal cavity findings, Ziv-aflibercept-related findings were reversible within 5 months after treatment cessation. In sexually immature monkeys treated for 3 months, the main compound-related findings were comparable to those in sexually mature monkeys.

Ziv-aflibercept was shown to induce a moderately delay in wound repair and healing from 0.3 mg/kg/administration after IV administration in rabbits. When administered IV to pregnant rabbits (as a 30 minute infusion once daily, on gestation Days 6, 9, 12, 15, and 18 - a total of 5 administrations) Ziv-aflibercept induced minimal to moderate maternal toxicity, abortion, and embryolethality at 60 mg/kg/administration. External, visceral,and/or skeletal malformations were observed in fetuses from pregnant rabbits treated from 3 mg/kg/administration (approximately 1.3 times the exposure in patients treated at the recommended human dose).

To date, Ziv-aflibercept has been administered to approximately 2000 patients with advanced solid malignancies in clinical oncology trials, to 76 healthy subjects, and to 41 ophthalmology patients. Doses have been administered up to 800 μg/kg subcutaneously (SC) twice weekly, 7 mg/kg IV every 2 weeks, and 9 mg/kg IV every 3 weeks.

Target pharmacological exposure has been reached at doses ≥2 mg/kg IV given every 2 weeks. Free Ziv-aflibercept levels have remained in excess of bound Ziv-aflibercept levels throughout the dosing intervals at this, or higher, doses. Objective tumor responses and prolonged (>1year) disease stabilization have been reported at dose levels ≥800 μg/kg SC and ≥1 mg/kg IV with Ziv-aflibercept monotherapy and with Ziv-aflibercept administered in combination with cytotoxic chemotherapy.

Phase 1 studies, as both single agent and combination chemotherapy, are ongoing. Phase 2 studies of Ziv-aflibercept, either alone or in combination with standard cytotoxic agents, are ongoingin a variety of oncologic indications. Phase 3 combination studies are ongoing in the following indications: lung cancer, colorectal cancer, pancreatic cancer, and prostate cancer. On August 3, 2012, the U.S. Food and Drug Administration (FDA) approved Ziv-aflibercept in combination with FOLFIRI for the treatment of patients with refractory colorectal cancer (following progression or resistance to an oxaliplatin based regimen).[20]

2.2 Neuroendocrine Tumors

NET's have been reported with increasing frequency from years 1973 and 2004; recent estimates are that the incidence of NETs is 5.25 per 100,000 population.[1] Moreover, because these tumors may be more indolent than other malignancies, the prevalence of patients diagnosed with NETs is estimated to be greater than 100,000 in the US.[1] The majority of NETs are carcinoid tumors, which most commonly arise in the bronchi, small intestine, appendix, or rectum.[2] Localized carcinoid tumors are treated with curative intent by surgical resection whenever possible. However, curative surgery is often not possible due to the presence of metastatic disease at diagnosis. The treatment of patients with advanced carcinoid tumors has been an area of intense investigation in recent years.[2]

The medical treatment of carcinoid tumors includes cytotoxic chemotherapy, biologic agents, and somatostatin analogs. In the past decade, investigators have explored a number of different cytotoxic chemotherapy regimens for this disease, with generally disappointing results. Agents such as docetaxel, irinotecan, cisplatin, and gemcitabine have all failed to demonstrate significant tumor response.[3-5] In an Eastern Cooperative Oncology Group (ECOG) Phase III study of chemotherapy in carcinoid tumors (E1281), patients were randomly assigned to treatment with 5-FU plus doxorubicin or 5-FU plus streptozocin.[6] The median PFS was 4.5 months for the 5-FU plus doxorubicin arm and 5.3 months for the 5-FU plus streptozocin arm. Overall survival durations recorded in this trial were also suboptimal, at 15 and 24 months respectively.

In the past year however, the treatment of advanced neuroendocrine tumors has undergone a rapid evolution. Initial phase II studies of sunitinib and everolimus suggested that these biologically targeted agents have antitumor activity in patients with advanced neuroendocrine tumors.[7-9] In patients with pancreatic neuroendocrine tumors, independent placebo-controlled randomized studies of the biologically targeted everolimus and sunitinib both revealed clear improvements in progression-free survival.[10,11] Based on the results of these studies, both everolimus and sunitinib were approved by the FDA for the treatment of advanced, progressive pancreatic neuroendocrine tumors in May, 2011. A randomized phase III study of Octreotide with or without everolimus in patients with advanced carcinoid tumors

(RADIANT 2) demonstrated an improvement in progression-free survival based on local investigator review, however did not meet its statistical endpoint which was based on central radiology review (Pavel, Hainsworth, Baudin, et al ESMO congress, 2010).

2.3 VEGF Inhibition in Carcinoid Tumors

While no large randomized studies have been completed, several early phase studies suggest that VEGF pathway inhibition is a promising approach in treating patients with advanced carcinoid tumors. Sunitinib, Sorafenib, and pazopanib have been evaluated in advanced carcinoid tumors in the phase II setting.[7,12,13] These drugs have been associated with low radiographic response rates, but a relatively high rate of disease stabilization and potentially encouraging progression-free survival durations. These observations suggest that they may have a cytostatic effect that is under-appreciated when radiographic response is used as the primary efficacy endpoint.

Phase II Studies of VEGF Pathway Inhibitors in Advanced Carcinoid

Agent	*No. Patients*	*Tumor Response Rate (%)*	*Median TTP or PFS*	*Reference*
Bevacizumab	22	18	14 mos	Yao et al. 2008
Sunitinib	41	2	10.2 mos	Kulke et al. 2008
Sorafenib	50	7	7.8 mos	Hobday et al 2007
Pazopanib	22	0	12.7 mos	Phan et al 2010

Bevacizumab has also been evaluated in a randomized phase II study of 44 patients with advanced or metastatic carcinoid tumors on a stable dose of octreotide. Patients were randomly assigned to 18 weeks of Bevacizumab or pegylated IFNa-2b, followed by treatment with both drugs.[14] During the first 18 weeks of therapy, four (18 percent) of the Bevacizumab-treated patients experienced radiographic partial responses; furthermore, 95 percent of patients treated with octreotide plus Bevacizumab remained progression-free, compared with only 68 percent of those receiving octreotide plus IFNa-2b. Based on these results, SWOG is leading a large, randomized study of Bevacizumab versus interferon in patients with advanced carcinoid tumors (S0518).

2.4 Role of Octreotide in Carcinoid Tumors

Octreotide is commonly used for the control of symptoms of hormonal hypersecretion in patients with advanced carcinoid tumors. Recent evidence also suggests that octreotide may slow tumor growth. In a recent study, 85 patients with metastatic midgut neuroendocrine tumors were randomized to receive either octreotide or placebo; the median TTP for patients receiving octreotide was 14.3 months as compared to 6 months for patients receiving placebo.[15] Recent studies evaluating novel agents in advanced carcinoid tumors have required concurrent octreotide to avoid the potential for confounding.[2]

2.5 Rationale

VEGF Trap (Ziv-aflibercept) is a recombinant protein consisting of the extracellular domains of VEGFR 1 and 2 fused to the Fc portion of immunoglobulin G1. Ziv-aflibercept compares favorably to other VEGF

inhibitors in preclinical studies, showing a high binding affinity for VEGF-A and other VEGF isoforms, as well as binding affinity for PlGF, which also contributes to angiogenesis.[16] Phase II studies of Ziv-aflibercept have shown preliminary evidence of activity in patients with advanced glioma, urothelial cancer, and treatment resistant lung cancer, utilizing a standard dose of 4 mg/kg administered intravenously every 2 weeks.[17-19]

In light of preliminary evidence of activity associated with VEGF inhibitors in carcinoid, as well as the significant unmet clinical need in this area, we propose a single-arm phase II study of Ziv-aflibercept in patients with advanced carcinoid tumors.

Because prior studies of targeted agents have demonstrated low RECIST-defined tumor response rates in advanced carcinoid, we propose using PFS as a primary endpoint. The RADIANT 2 study will be used as the primary benchmark to assess median PFS durations that would be expected with an active targeted agent or with octreotide alone in this patient population (Pavel, Hainsworth, Baudin, et al ESMO congress, 2010). Entry criteria for our study will closely parallel those used for the previously reported RADIANT 2 study: patients will be required to have low or intermediate grade tumors and evidence of disease progression within 12 months prior to study enrollment. Concurrent treatment with octreotide will also be required.

2.6 Study design

Among the first 10 patients with advanced carcinoid tumors treated with Ziv-aflibercept at a dose of 4 mg/kg intravenously every 2 weeks, nine developed grade 3 or higher hypertension. The protocol has been modified to decrease the starting dose of aflibercept to 2 mg/kg intravenously every 2 weeks for any patients enrolling after July 15, 2014. Any patients enrolled prior to July 15, 2014 may continue dosing at their current tolerated dose level.

3. Participant Selection

3.1 Inclusion Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Participants must have histologically confirmed well differentiated or moderately differentiated neuroendocrine tumor from either a primary or metastatic site. Carcinoid tumors of any primary site are eligible.

3.1.2 Participants must have disease that is not amenable to curative resection.

3.1.3 Participants must have evidence of disease progression within 12 months prior to study entry.

3.1.4 Participants must have measurable disease. (RECIST 1.1)

3.1.5 Prior chemoembolization of local ablative therapies are allowed, provided there is measurable disease outside of the area treated, or documented evidence of progression at the site of prior treatment.

3.1.6 There is no limit to number of prior treatments. Prior bevacizumab is allowed unless it was discontinued due to unacceptable toxicity. Prior therapy with tyrosine kinase inhibitors (TKI) targeting VEGF receptors is allowed.

3.1.7 Treatment with a somatostatin analog (e.g., octreotide acetate) is required for all participants. Octreotide naive patients may initiate this during the screening period or at start of study.

3.1.8 Prior treatment including chemoembolization or other ablative therapy, any cytotoxic, biologic or other investigational agents must have been completed at least 4 weeks prior to study entry.

3.1.9 Prior palliative radiation must have been completed at least 2 weeks prior to study entry.

3.1.10 Age is $\geq$ 18 years

3.1.11 ECOG performance status $\leq$1

3.1.12 Participants with a history of hypertension must be adequately controlled with antihypertensive medication and BP must be less than 140/90 mmHg prior to initiation of Ziv-aflibercept.

3.1.13 Therapeutic anticoagulation is allowed. The participant must be on a stable dose of anticoagulant medication (warfarin, or LMWH) prior to study entry.

3.1.14 Any major surgery must be completed at least 4 weeks prior to study entry. Minor surgical procedures (except insertion of vascular access device) must have been completed at least 2 weeks prior to study entry.

3.1.15 Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry,for the duration of study participation,and for 3 months after last administration of Ziv-aflibercept. Women of child bearing potential must have a negative pregnancy test (urine or blood) within 14 days of registration.

3.1.16 Participants must have organ and marrow function as defined below:

- Absolute neutrophil count $\geq$ 1,500/mcL
- Hemoglobin >9g/dL
- Platelets $\geq$ 100,000/mcL

- total bilirubin ≤ 1.5X upper limit of normal
- AST (SGOT)/ALT (SGPT) ≤ 2.5 X upper limit of normal or ≤5 X upper limit of normal if liver metastases are present.
- Alkaline Phosphatase ≤ 5X upper limit of normal
- Creatinine ≤ 1.5X upper limit of normal
- Urine protein/creatinine ratio of less than 1.

3.1.17 Participant is able to understand and comply with study requirements and is willing to sign a written informed consent document.

3.2 Exclusion Criteria:

Participants who exhibit any of the following conditions at screening will not be eligible to participate in the study.

3.2.1 Poorly differentiated carcinoma, high grade neuroendocrine tumor or small cell carcinomas are excluded from this study.

3.2.2 Prior treatment with Ziv-aflibercept is not allowed.

3.2.3 Pancreatic neuroendocrine tumors (islet cell carcinoma) will be excluded from this study. All non functional and functional islet cell carcinomas such as insulinoma, glucagonoma, gastrinoma, VIPoma will be excluded.

3.2.4 No other investigational, biologic or chemotherapy agents, localized ablation or chemoembolization for 4 weeks prior to study entry.

3.2.5 Participant has not adequately recovered from toxicity of previous therapy.

3.2.6 Participants with known untreated brain or other central nervous system metastases are excluded.

3.2.7 Pregnant or nursing mothers are excluded.

3.2.8 Known allergy to any of the study agents or to compounds of similar chemical or biologic composition are excluded (including other somatostatin analogs).

3.2.9 Participants with a history of congestive heart failure (NYHA class II, III or IV) are excluded

3.2.10 No symptomatic peripheral arterial disease

3.2.11 No unhealed wounds, ulcers or bone fractures

3.2.12 No known HIV positive, or active Hepatitis infection

3.2.13 No history of abdominal fistula, GI perforation, intra abdominal abscess, uncontrolled GI bleeding, diverticulitis within 6 months of study entry.

3.2.14 No history of arterial thrombotic events such as MI (myocardial infarction), unstable angina pectoris or any ischemic or hemorrhagic CVA (cerebrovascular accident) within past 6 months

3.2.15 Participants with history of pulmonary embolism, DVT, or vascular access related thrombosis will be allowed on study provided they are receiving adequate anticoagulation at a stable dose at the time of study entry.

3.2.16 No history of prior or synchronous malignancy, except;

- Prior malignancy was treated with curative intent and there is no known active disease present for greater than or equal to 3 years prior to study entry
- Participants with adequately treated non-melanoma skin cancers, cervical carcinoma in situ, or prostatic intraepithelial neoplasia without evidence of prostate cancer are eligible.

3.2.17 Any uncontrolled non-malignant illness that in the opinion of the treating investigator may increase the risks associated with study participation or may interfere with the conduct of the study or interpretation of study results would exclude the participant.

3.2.18 Uncontrolled psychiatric illness or social situations that would limit compliance with study requirements would exclude the participant.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Eligible participants will be registered through the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of study related treatment.

A designated member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator, Jennifer Chan, MD, MPH or the DFCI study team.

If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

3. Fax the eligibility checklist and all pages of the consent form to the QACT at 617-632-2295.

   The QACT Registrar will validate eligibility and register the participant.

4. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis, however if necessary, treatment may be administered while inpatient at Brigham and Women's Hospital or Massachusetts General Hospital.

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Ziv-aflibercept is commercially available, however, for this study it will be provided free of charge by the sponsor Sanofi-Aventis.

Octreotide is commercially available (generic octreotide acetate for subcutaneous injection and Sandostatin LAR depot®). It is FDA approved and will not be provided by the study.

All patients will be receiving concurrent octreotide while on this study. Refer to guidelines below for initiating treatment for octreotide naive patients. **Octreotide and Ziv-aflibercept do NOT have to be administered on the same day.**

Table: 2 **STUDY AGENT**	**Starting Dose**	**Administration** **(28 day cycles)** **(+/-3days is allowed)**
Ziv-aflibercept	Patients enrolled prior to July 15, 2014: **4mg/kg** Patients enrolled after July 15, 2014: **2mg/kg**	**Intravenously: over 1 hour every 2 weeks**
Octreotide LAR **(**commercially available as Sandostatin LAR® depot)	**Recommended starting dose 20 mg**	**IM: Every 4 weeks** Refer to section 5.1

**Patients enrolled prior to July 15, 2014 may continue on their current tolerated dose.*

5.1 Patient enrollment

To ensure patient safety and to fully assess for adverse events, patients will be enrolled in cohorts consisting of 3 patients. If all 3 patients in each cohort are able to complete one full cycle of therapy without unmanageable toxicity, an additional 3 patients will be enrolled to another patient cohort. Enrollment in cohorts of 3 patients and evaluation of adverse events once each cohort has completed one cycle of therapy will continue until accrual has been completed.

5.2 Octreotide Guidelines (naïve patients)

For octreotide naive patients, a suggested test dose of subcutaneous octreotide acetate 150 mcg is administered under supervision in clinic and is followed by a minimum of one hour of observation to

assess for adverse reaction. If the test dose is tolerated, the first octreotide LAR depot injection (suggested dose 20 mg IM) may be administered anytime following the minimum period of observation.

The dose and frequency of administration of octreotide may vary according to treating investigator discretion and symptom management of the study participant. The suggested starting dose and schedule is noted above. If study participant has been on a stable dose prior to study entry, they are to continue with that dose and schedule. Ziv-aflibercept and octreotide do not have to be administered on the same day.

5.3 Pre-treatment Criteria:

5.3.1 Screening (within 28 day of day 1 unless otherwise noted)

- CT or MRI scans of chest, abdomen and pelvis with contrast (treating investigators discretion). The same modality must be used throughout the study.
- Informed consent/Confirmation of eligibility
- Medical History, Physical examination, ECOG
- Vital Signs, height and weight
- Pregnancy test within 14 days for all women of childbearing potential (urine or serum)
- EKG
- Screening labs will include CBC with differential, Comprehensive chemistry panel, , U/A, UPCR.
- Serum Chromogranin A and 24 hour urine collection for 5HIAA.

  (During the screening period, give patient supplies and instructions for collection of 24 hour urine for 5HIAA and advise patient to return specimen on C1D1 or before). If results of these are normal at baseline, do not repeat while on study. If above institutional ULN at baseline, perform at the time of tumor restaging.

- May receive test dose of subcutaneous octreotide acetate anytime during screening period or on C1D1 if octreotide naive.

5.3.2 Cycle 1 Day 1:

If screening labs are done within 14 days of day 1, do not repeat on C1D1, otherwise perform the following:

- CBC with differential, comprehensive chemistry panel, U/A and UPCR
- Study Blood samples (Optional)
- Return 24 hour urine collection for 5HIAA
- Physical Exam, ECOG
- Baseline symptom and toxicity assessment
- Pre treatment Vital Signs and weight
- Blood Pressure monitor will be given to patient for use at home.
- Vital Signs 1 hour after first dose of Ziv-aflibercept (just prior to leaving infusion unit)

5.3.3 **Cycle 1 Day 3 (+/- 2 days)**

- Vital signs
- Physical exam, ECOG
- Toxicity assessment

5.3.4 **Day 1 of all subsequent cycles (refer to study calendar, section 8):**

- CBC with differential, comprehensive chemistry panel
- Pre-dose study blood sample (optional)
- Physical exam, ECOG
- Toxicity assessment
- Vital signs, weightPregnancy test for sexually active women of childbearing potential (urine or serum)
- +/- 3 days **for all study assessments and treatment** is allowed
- U/A and Urine Protein/creatinine ratio every other cycle

5.1.4: **Day 15 of all cycles:**

- CBC with differential, comprehensive chemistry panel

- Toxicity assessment
- Vital signs, weight
- +/- 3 days for all study assessments and treatment is allowed

5.1.5: **Tumor Assessment/Other**:

- Restaging scans will be performed every 12 weeks.
- If baseline levels of serum chromogranin A and/or Urinary 5HIAA levels were greater than institutional ULN these tests will be repeated at time of restaging.

5.1.6: Blood Pressure Monitoring at home:

Hypertension is a common side effect experienced by patients receiving Ziv-aflibercept. For the first 3 cycles, patients will check their blood pressure once daily using a home automated blood pressure cuff (provided by study). After the first 3 cycles, investigator's discretion may be used to determine if blood pressure monitoring at home is still necessary. Blood pressure will be recorded in diary (Appendix C) which will be returned to the study team at each visit for the first three cycles. Patients will be advised to contact the study investigator of designee for new or worsening hypertension to allow rapid implementation of antihypertensive therapies.

5.4 Agent Administration

5.4.1 **Ziv-aflibercept:**

Ziv-aflibercept is administered intravenously over approximately 1 hour via peripheral vein or central venous catheter using an institution approved infusion pump. The infusion duration should not exceed 2 hours. Following the first infusion of Ziv-aflibercept, patient should be observed in clinic for 1 hour post infusion. Vital signs will be observed anytime pre-dose for all infusions and immediately prior to discharge from infusion unit following the first infusion only.

Pre medication is not required prior to the administration of Ziv-aflibercept.

In the event of reaction, subsequent infusions will be up to the discretion of the treating investigator and protocol guidelines. For subsequent infusions, pre-medications may include but are not limited to acetaminophen, meperidine, steroids, diphenhydramine, or H2 blockers. These may be used at the investigators discretion as there is no recommended regimen of pre medication established.

5.4.2 **Octreotide**

Octreotide is administered by injection: as short acting "test dose" (subcutaneous) or long acting LAR (intramuscular).

Octreotide is commercially available as generic octreotide acetate (used in this study for subcutaneous administration) or Sandostatin LAR® depot.

Sandostatin LAR® depot (octreotide acetate for injectable suspension) will be administered intramuscular (gluteus muscle) by injection. It is available in single use kits containing a 5 mL vial of 10 mg, 20 mg or 30 mg strength, a 2 mL vial of diluent, a 5 mL sterile plastic syringe, two sterile 1½" 19 gauge needles, and three alcohol wipes.

Sandostatin LAR® depot drug product kit will be brought to room temperature for a 30-60 minute period prior to preparation of the drug suspension. An instruction booklet for the preparation of drug suspension for injection is also included with each kit. Follow package insert and standard institutional practice for administration and preparation.

5.5 General Concomitant Medication and Supportive Care Guidelines

- All concomitant medications will be recorded in the medical record. Medication list will be reviewed and updated at the time of screening and monitored throughout study. There are no prohibited medications.
- The use of antiemetic and other supportive care medications will be at the treating investigators discretion
- Pre medication prior to first dose of Ziv-aflibercept is not required or recommended.
- In the event of allergic reaction or anaphylaxis the infusion is to be immediately suspended and symptomatic and supportive treatment will be administered according to institutional standards.
- Palliative radiation will not be allowed while on study.
- Patients with known history of hypertension will continue on antihypertensive regimens as prescribed. Modify antihypertensive drug therapy based on recommendations in the table (section 6.4).
- Transfusions of blood products will be allowed if necessary
- The use of growth factors will not be allowed.
- The use of herbal supplements or high dose vitamins is not recommended as the interactions are not known.

5.6 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Evidence of disease progression per RECIST criteria 1.1
- Intercurrent illness that prevents further administration of treatment
- Unacceptable toxicity or other adverse events
- Participant decides to withdraw consent from the study
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.
- Grade 3 or 4 allergic or anaphylactic reaction to Ziv-aflibercept
- Investigator Discretion

5.7 Duration of Follow Up

The length of follow-up for the study is two years. After removal from study, participants will be followed during this period for survival approximately every 3 months until death or until loss to follow-up. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.8 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.5 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (eCRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating sub investigators must immediately notify Jennifer A. Chan, MD, MPH via email or phone.

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Common Toxicity Criteria for Adverse events (CTCAE) Version 4.0 will be used for toxicity assessment and grading.

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit.

Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities

A list of the expected or known adverse events and potential risks associated with the study agents are listed below. Assessment of toxicity will be determined by the treating investigator or designee, using CTCAE version 4.0. Recommendations for dose delay or modification are

noted in the protocol in section 6.3. The definition of adverse or serious adverse event and reporting guidelines are defined in section 10 of this protocol.

ZIV-AFLIBERCEPT:

- **Hematological**: anemia, thrombocytopenia, thrombotic microangiopathy. When used in combination with cytotoxic chemotherapy: neutropenia, febrile neutropenia, neutropenic colitis and sepsis
- **Cardiac**: cardiac failure, hypertension
- **Digestive toxicity**: abdominal pain, GI hemorrhage, intestinal perforation, intestinal obstruction, enteric fistula, peritonitis, pneumatosis intestinalis, nausea, vomiting , diarrhea, constipation, mucosal inflammation or ulceration, stomatitis, hepatic enzymes increased
- **General disorders**: asthenia, fatigue, musculoskeletal pain, injection site reaction
- **Immune system disorders**: hypersensitivity
- **Metabolic disorders**: dehydration
- **Musculoskeletal**: arthralgia, myalgia, osteonecrosis
- **Nervous system**: headache, dizziness, encephalopathy, RPLS, cerebral ischemia, cerebral hemorrhage, cerebral venous thrombosis
- **Renal disorders**: proteinuria, hematuria, renal failure
- **Respiratory disorders**: dysphonia, dyspnea, epistaxis, hemoptysis, pulmonary embolism, tracheo-esophageal fistula
- **Skin disorders**: (seen in combination with cytotoxic chemotherapy) palmar/plantar erythrodysaesthia syndrome, erythema
- **Vascular disorders**: hypertension, deep vein thrombosis and phlebitis
- **Wound healing impairment.**

6.1.1 **OCTREOTIDE LAR**: (refer to package insert Sandostatin LAR® depot)

- **Gallbladder** abnormalities, especially stones and/or biliary sludge, frequently develop in patients on chronic Octreotide acetate therapy.

- **Sinus bradycardia** developed in 25%; conduction abnormalities occurred in 10% and arrhythmias developed in 9% of patients during Octreotide acetate therapy.

- **Diarrhea**, loose stools, nausea and abdominal discomfort. Vomiting, flatulence, abnormal stools, abdominal distention, and constipation were each seen in less than 10% of patients.

- In rare instances, **gastrointestinal side effects** may resemble acute intestinal obstruction, with progressive abdominal distention, severe epigastric pain, abdominal tenderness and guarding.

- **Hypoglycemia and hyperglycemia** occurred in 3% and 16% of acromegalic patients, respectively, but only in about 1.5% of other patients. Symptoms of hypoglycemia were noted in approximately 2% of patients.

- **Hypothyroidism**: In acromegalics, biochemical hypothyroidism alone occurred in 12% while goiter occurred in 6% during Octreotide acetate therapy. In patients without acromegaly, hypothyroidism has only been reported in several isolated patients and goiter has not been reported.

- Other adverse events: **pain on injection** was reported in 7.7%, headache in 6% and dizziness in 5%. Pancreatitis was also observed.

- **Rare adverse events** (relationship to drug not established), each observed in 1%–4% of patients, included fatigue, weakness, pruritus, joint pain, backache, urinary tract infection, cold symptoms, flu symptoms, injection site hematoma, bruise, edema, flushing, blurred vision, pollakiuria, fat malabsorption, hair loss, visual disturbance and depression.

- **Events reported in less than 1% of patients and for which relationship to drug is not established are listed:** Gastrointestinal: hepatitis, jaundice, increase in liver enzymes, GI bleeding, hemorrhoids, appendicitis, gastric/peptic ulcer, gallbladder polyp; Integumentary: rash, cellulitis, petechiae, urticaria, basal cell carcinoma; Musculoskeletal: arthritis, joint effusion, muscle pain, Raynaud's phenomenon; Cardiovascular: chest pain, shortness of breath, thrombophlebitis, ischemia, congestive heart failure, hypertension, hypertensive reaction, palpitations, orthostatic BP decrease, tachycardia; CNS: anxiety, libido decrease, syncope, tremor, seizure, vertigo, Bell's Palsy, paranoia, pituitary apoplexy, increased intraocular pressure, amnesia, hearing loss, neuritis; Respiratory: pneumonia, pulmonary nodule, status asthmaticus; Endocrine: galactorrhea, hypoadrenalism, diabetes insipidus, gynecomastia, amenorrhea, polymenorrhea, oligomenorrhea, vaginitis; Urogenital: nephrolithiasis, hematuria; Hematologic: anemia, iron deficiency, epistaxis; Miscellaneous: otitis, allergic reaction, increased CK, weight loss.

- **Anaphylactoid reactions**, including anaphylactic shock

6.2 Toxicity Management:

Treatment with Ziv-aflibercept may continue if the following criteria are met. Treatment may be delayed for a maximum of four weeks.

- Absolute neutrophil count ≥ 1,000/mcL
- Platelets ≥ 50,000/mcL
- Creatinine ≤ 1.5X upper limit of normal
- Urine protein: Refer to section 6.6 for specific guidelines.
- BP: Refer to BP management guidelines in section 6.4.
- Resolution of clinically significant non-hematological toxicity to baseline or ≤ Grade 1 (clinical significance will be determined by the treating investigator)
- ECOG 2 or less

6.3 Hypersensitivity Reaction or Anaphylaxis

CTCAE version 4.0 Definitions	Grade 1	Grade 2	Grade 3	Grade 4
Allergic Reaction	Transient flushing or rash, drug fever (<100.4° F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated.
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated.
Action to be taken	Continue infusion and monitor vital signs, administer supportive care per treating investigators discretions.	Immediately interrupt infusion and provide supportive care according to institutional standards Upon recovery may re challenge at treating investigators discretion.	Immediately interrupt infusion and provide supportive care according to institutional standards **Off study**	Immediately interrupt infusion and provide supportive care according to institutional standards **Off study**

6.4 Management of hypertension:

Hypertension is a common side effect experienced by patients receiving Ziv-aflibercept.

Due to the incidence of hypertension that has been observed in patients with carcinoid tumors treated with aflibercept, ***prophylactic antihypertensive therapy*** with lisinopril 10 mg daily should be considered for patients with no contraindication to use of an ACE inhibitor. If lisinopril is not started prophylactically, initiation of another antihypertensive agent prior to treatment with aflibercept can be considered as clinically appropriate.

For patients already on antihypertensive medication, current therapy will be continued.

For all patients, blood pressure will be monitored closely at home and at a clinic visit on C1D3 (+/- 2 days) so that medications can be titrated as needed to keep systolic BP < 140 and diastolic BP < 90.

Blood pressure and dosing of aflibercept will be managed as follows:

Hypertension CTCAE version:4.0	**Definition**	**Recommended management**
Grade 1	Prehypertension: systolic 120-139 mm Hg or diastolic 80-89 mm Hg	No dose modification or delay
Grade 2	Stage 1 hypertension: systolic: 140-159 mm Hg **or** diastolic: 90-99 mm Hg • Medical intervention indicated • Recurrent or persistent (≥24 hours) • Symptomatic increase by >20 mmHg (diastolic) • >140/90 mm Hg if previously wnl • Monotherapy indicated	No dose modification or delay • Increase current antihypertensive medication or consider addition of an additional agent, such as ACE inhibitor, labetalol or amlodipine.
Grade 3	Stage 2 hypertension: Systolic ≥160 mm Hg or Diastolic ≥100 • Medical intervention indicated • More than one antihypertensive drug • **or** more intensive therapy than previously indicated	Delay treatment with Ziv-aflibercept for a maximum of 4 weeks. • Increase current antihypertensive medication or consider addition of an additional agent, such as ACE inhibitor, labetalol or amlodipine. First occurrence: When BP is controlled to < 140/90, resume Ziv-aflibercept at same dose.

		Second occurrence: When BP is controlled to < 140/90 resume Ziv-aflibercept at reduced dose level. Third occurrence: Off study
Grade 4	Life threatening consequences (e.g., malignant hypertension, transient or permanent neurological deficit, hypertensive crisis); urgent intervention indicated	Ziv-aflibercept: Off Study

*** Suggested antihypertensive medications**

Agent	**Usual starting dose and frequency**	**Usual dose range**
Combined alpha and beta blockers		
Labetalol	100 mg twice daily	200 – 800 mg
Angiotensin converting enzyme inhibitors		
Lisinopril	10 mg once daily	5- 40 mg
Dihydropyridine (DHP) Calcium Channel Blockers		
Amlodipine	5 mg once daily	2.5-10 mg

Adapted from Maitland et al, JNCI, 2010 May 5;102(9):596-604.

6.5 Home Blood Pressure Monitoring

For the first 3 cycles, patients will check their blood pressure daily using a home automated blood pressure cuff (provided by study). After the first 3 cycles, investigator's discretion may be used to determine if blood pressure monitoring at home is necessary.

Blood pressure will be recorded in diary (Appendix C) and returned to the study team at each visit for the first three cycles. Patients will be advised to contact the study investigator or designee for new or worsening hypertension to allow rapid implementation of antihypertensive therapies.

6.6 Thromboembolic events

CTCAE version 4.0	Grade 1	Grade 2	Grade 3	Grade 4
Thromboembolic events	Venous thrombosis (e.g., superficial thrombosis)	Venous thrombosis (e.g., uncomplicated DVT), medical intervention indicated	Thrombosis (e.g., uncomplicated pulmonary embolism [venous], non embolic cardiac mural [arterial] thrombosis), medical intervention indicated	Life threatening (e.g., pulmonary embolism, CVA, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated
Action to be taken	Continue Ziv-aflibercept at investigator's discretion		Delay treatment with Ziv-aflibercept for maximum of four weeks. Resume when medically stable and on stable dose of anticoagulation at same dose.	Off study

6.7 Proteinuria:

Toxicity/CTCAE version 4.0	Grade 1	Grade 2	Grade 3	Nephrotic Syndrome
Proteinuria	1+ proteinuria; Urinary protein <1g/24 hours	2+ proteinuria; Urinary protein 1-3.4g/24 hours	Urinary protein >3.5g/24 hours	
Actions to be taken	Continue Ziv-aflibercept	• **UPCR ≤1.9**: continue Ziv-aflibercept. • **UPCR > 1.9: hold Ziv-aflibercept and collect** a 24 hour urine sample for urinary **protein** prior to next visit. Resume Ziv-aflibercept if urinary protein is < 2 gms/24hours and UPCR is **≤1.9** First occurrence: upon recovery resume at current dose Second occurrence: upon recovery reduce dose of Ziv-aflibercept Third occurrence: off study	Hold Ziv-aflibercept for a maximum of four weeks Perform 24 hour urine collection for protein weekly. Resume Ziv-aflibercept at reduced dose if resolution of urinary protein to <2g/24 hours and UPCR is **≤1.9** Consider nephrology consult	Off study Consider nephrology consult

*Urine Protein Creatinine Ratio. UPCR=Protein/creatinine. Obtain at least 4 ml of a random urine sample. Determine urine protein concentration (mg/dL) and urine creatinine concentration (mg/dL). Divide results of protein concentration by creatinine concentration.

6.8 Other non-hematological toxicity:

Toxicity/CTCAE version 4.0	Grade 1 or 2	Grade 3	Grade 4
Hemorrhage **(Except intracranial hemorrhage)**	Mild or moderate; self limited; intervention may or may not be indicated (e.g., cauterization	Requiring transfusion, radiologic, endoscopic or operative intervention	Life threatening and urgent intervention indicated
Actions to be taken	Medically manage and continue Ziv-aflibercept at investigators discretion	Off Study	Off study
Other:			
Abdominal fistula or wound dehiscence **Intracranial hemorrhage** **GI perforation** **Reversible Posterior Leukoencephalopathy syndrome (RPLS)** **Arterial Thrombotic Events**	Any Grade: Off Study		

6.9 Dose Modifications/Delays

Dose modification or delay will be based on clinically significant, study drug related toxicity as determined by treating investigator. Toxicity will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

For hematological toxicity, any dose modification or delay will be based on results obtained on day of treatment (e.g., day 1 or 15 of each cycle).

For non-hematological toxicity, any dose modification or delay or will be based on the worst grade of the toxicity that occurred at any time, and is thought to be related to Ziv-aflibercept and clinically significant.

Once a dose has been attenuated to dose level -1 (1 mg/kg), there will be no re-escalation allowed. If dose level -1 is not tolerated, the patient will be discontinued from study treatment. For patients enrolled prior to July 15, 2014, reduction to dose level -2 (1 mg/kg) will be allowed. Treatment with Ziv-aflibercept may be delayed for a maximum of 4 weeks.

Patients enrolled prior to July 15, 2014:

Dose modification table:	Starting dose	Dose -1	Dose -2
Ziv-aflibercept	4 mg/kg	2 mg/kg	1 mg/kg

Patients enrolled after July 15, 2014:

Dose modification table:	Starting dose	Dose -1
Ziv-aflibercept	2mg/kg	1 mg/kg

7. DRUG FORMULATION AND ADMINISTRATION

7.1 Ziv-aflibercept:

7.1.1 Description

Concentrate for solution for IV infusion: Ziv-aflibercept is supplied for IV administration as a sterile, non-pyrogenic, colorless to pale-yellow colored, 25 mg/mL solution, 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. The pH of the solution is about 6.2. The aqueous 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.

One Ziv-aflibercept drug product presentationis available:
200 mg/8 mL in a 10 mL vial

The fill volume has been established to ensure removal of 8 mL, respectively.
Prior to infusion, the Ziv-aflibercept dosage form must be diluted directly into infusion bags of 0.9% sodium chloride solution or 5% dextrose to a final volume of 100ml. 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.
Ziv-aflibercept does not contain any microbial preservative. Therefore, care must be taken to ensure the sterility of the prepared solution. The dilution must be carried out by a healthcare professional under aseptic conditions

7.1.2 **Storage and Stability**

Clinical supplies as packaged should be stored under refrigerated conditions (2 to 8°C).
Stability studies on Ziv-aflibercept concentrate for solution for infusion are ongoing to ensure that clinical supplies remain within specifications during the duration of the clinical study.

Based on available stability data, the concentrate for solution for infusion in its original unopened container is stable for 36 months under the recommended storage conditions.

7.1.3 **Compatibility**

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Dilution under aseptic conditions should be applied. Chemical and physical real-time stability of dilute Ziv-aflibercept solutions at 0.6 to 8 mg/mL has been demonstrated for up to 24 hours under refrigerated conditions (2 to 8°C) or up to 8 hours at ambient temperature (approximately 25°C) in polypropylene syringes or in infusion bags made of the following materials: polyvinyl chloride (PVC) containing di (2-ethylhexyl) phthalate (DEHP) polyolefin (PVC free DEHP free)

Diluted solutions of Ziv-aflibercept should be administered using infusion tubing made of the following materials:

- PVC containing DEHP
- DEHP free PVC containing tris(2-ethylhexyl)trimellitate (TOTM)
- polypropylene
- polyethylene lined PVC
- polyurethane

The infusion sets must contain a 0.2 μm polyethersulfone inline filter. Polyvinylidene fluoride (PVDF) filters and Nylon filters should not be used.

Infusions will be administered via the institution approved IV infusion pump using

administration sets made of the above materials.

Ziv-aflibercept will be infused over approximately 1 hour, via peripheral or central venous catheter using infusion pump. **The duration of the infusion should not exceed two hours at room temperature (approximately 25°C).**

7.1.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

7.1.5 Availability

- Ziv-aflibercept will be provided from the commercial supply, free-of-charge to study participants from Sanofi-Aventis.

- Octreotide acetate LAR depot and subcutaneous octreotide acetate are commercially available and will not be paid for by this study as they are considered to be standard of care.

7.1.6 Administration

Ziv-aflibercept will be infused over 1 hour, via peripheral or central venous catheter using infusion pump. The duration of the infusion should not exceed two hours at room temperature (approximately 25°C).

7.1.7 Ordering

Ziv-aflibercept will be ordered directly from Sanofi-Aventis by the assigned research pharmacist.

7.1.8 Accountability

The responsible research pharmacist will maintain a record of the inventory and disposition of Ziv-aflibercept using the NCI Drug Accountability Record or institutional approved drug accountability form.

7.1.9 Destruction and Return

At the end of the study, any unused supplies of Ziv-aflibercept will be destroyed according to institutional policies or returned to Sanofi-Aventis. Destruction will be documented in the Drug Accountability Record Form.

7.2 Octreotide

US brand names: Octreotide acetate; Sandostatin® Sandostatin LAR® Depot
Information available in package insert.

7.2.1 **DESCRIPTION**

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

Sandostatin LAR® depot (octreotide acetate for injectable suspension) is available in a vial containing the sterile drug product, which when mixed with diluent, becomes a suspension that is given as a monthly intragluteal injection. The octreotide is uniformly distributed within the microspheres which are made of a biodegradable glucose star polymer, D,L-lactic and glycolic acids copolymer. Sterile mannitol is added to the microspheres to improve suspendability.

Octreotide LAR depot is available as sterile 5 mL vials in 3 strengths delivering 10 mg, 20 mg or 30 mg octreotide free peptide.

7.2.2 **Formulation:**

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

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

7.2.3 PHARMACOLOGY

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

In patients with acromegaly, the octreotide concentrations after single doses of 10 mg, 20 mg, and 30 mg octreotide LAR depot were dose proportional. The transient day 1 peak, amounting to 0.3 ng/mL, 0.8 ng/mL, and 1.3 ng/mL, respectively, was followed by plateau concentrations of 0.5

ng/mL, 1.3 ng/mL, and 2.0 ng/mL, respectively, achieved about 3 weeks post injection. These plateau concentrations were maintained for nearly two weeks. Following multiple doses of octreotide LAR depot given every 4 weeks, steadystate octreotide serum concentrations were achieved after the third injection. Concentrations were dose proportional and higher by a factor of approximately
1.6 to 2.0 compared to the concentrations after a single dose. The steady-state octreotide concentrations were 1.2 ng/mL and 2.1 ng/mL, respectively, at trough and 1.6 ng/mL and 2.6 ng/mL, respectively, at peak with 20 mg and 30 mg octreotide LAR depot given every 4 weeks. No accumulation of octreotide beyond that expected from the overlapping release profiles occurred over a
duration of up to 28 monthly injections of octreotide LAR depot. With thelongacting depot formulation octreotide LAR depot administered IM every 4 weeks the peak-to-trough variation in octreotide concentrations ranged from 44 to 68%, compared to the 163 to 209% variation encountered with the daily subcutaneous t.i.d. regimen of Sandostatin® Injection solution.

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

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

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

7.2.4 **Storage:**

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

However, after preparation, the drug suspension must be administered immediately.

8. STUDY CALENDAR:

*Each cycle is 28 days (+/- 3 days is allowed for all study related labs and treatment)	**Screening**[1]	**C1D1**[2]	**C1D3 (+/- 2 days)**	**C1D15**	**C2 and subsequent cycles**		**Following every 2 cycles**	**Following every 12 weeks**	**End of Study**
					D1	D15			
Medical History	x								
Physical Exam and ECOG PS	x	x	x		x				
Vital Signs/Height[3]/Weight	x	x	x	x	x	x			x
EKG	x								x
Pregnancy Test[4]	x				x				
Hematology[5]	x	x		x	x	x			x
Chemistry[6]	x	x		x	x	x			x
Urinalysis and Urine Protein/Creatinine ratio (UPCR)[7]	x						x[7]		
Imaging/tumor assessment [8]	x							x	
Chromogranin A /Urinary 5-HIAA (24 hr urine)[9]	x							x	

[1] Screening period is within 28 days of start
[2] Cycle 1 Day 1 labs do not need to be repeated if done within 14 days of start.
[3] Height is only required at screening.
[4] Urine or serum pregnancy test. For women of childbearing potential only. Day 1 of each cycle.
[5] CBC with differential
[6] Comp Chemistry Panel: lytes, BUN, creatinine, Calcium, glucose, albumin, ALT, total protein, total bilirubin, AST, alk phos.
[7] U/A and UPCR required every other cycle.
[8] Restaging scans will occur after every 3 cycles of aflibercept, (e.g., within 1 week prior to start of cycles 4, 7, 10, etc).
[9] Assessment of chromogranin A and urinary 5-HIAA will occur after every 3 cycles of aflibercept at the time of restaging scans. Assessment is required only if chromogranin A and urinary 5-HIAA are elevated at baseline.

Study Blood Collection[10]		x							
Concomitant Medication Monitoring		x →							x
Toxicity Assessment/AE monitoring		x	x →						x
Ziv-aflibercept		x		x	x	x			
Octreotide LAR depot[11]		x			x				
Home Blood Pressure Monitoring and Diary		x		x	x[12]	x			

9. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, participants with measurable disease will be assessed by RECIST 1.1 criteria. For the purposes of this study, participants should be reevaluated prior to every 4th cycle.

9.1 Antitumor Effect– Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every after 3 cycles of Ziv-aflibercept (approximately 12 weeks).

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response. Response rates will be calculated based on an intent-to-treat analysis that includes all patients who have received at least one dose of study treatment. Participants will have their response classified according to the definitions stated below.

9.1.1 Disease Parameters

Measurable disease. Measurable disease is the presence of at least one (1) lesion that can be accurately measured in at least one dimension with longest diameter ≥20 millimeters (mm) using conventional techniques (CT, MRI, x-ray) or ≥10 mm with spiral CT scan. Measurable lesions must be at least 2 times the slice thickness in mm.

[10] Refer to Appendix B for specific collection/storage information

[11] Octreotide schedule may vary according to patient needs or treating investigator discretion. Patients do not need to receive Octreotide and Ziv-aflibercept on the same day.

[12] Required through the first three cycles only. Home blood pressure monitory after the 3rd cycle of aflibercept will be performed at investigator discretion.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

A lesion in a previously irradiated or embolized area is not eligible for measurable disease unless there is objective evidence of progression of the lesion prior to study enrollment. Lesions in previously irradiated areas must be clearly identified as such.

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 < 15mm short axis, are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques, and cystic lesions are all considered non-measurable.

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. Lesions must be accurately measured in 1 dimension with a minimum size of 10 mm by CT or MRI (slice thickness no greater than 5 mm), 20 mm by *chest* x-ray. Nodes must have a short axis ≥ 15 mm. The short axis should be included in the sum of the lesions in the calculation of response. Nodes that shrink to < 10 mm are considered normal. Target lesions should be selected on the basis of their size, be representative of all the involved organs, and should be lesions that can be followed with reproducible repeated measurements.

Lytic bone lesions or mixed lytic-blastic lesions, *with identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered target lesions if the *soft tissue component* meets the definition of measurability as defined above. Cystic lesions thought to represent cystic metastases can be considered as target lesions. However, if non-cystic lesions are present, these are preferred for selection as target lesions. Lesions in previously irradiated areas or areas subject to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression of that lesion.

Non-target lesions.

All other lesions, including small lesions < 10 mm or pathological lymph nodes measuring ≥ 10 mm to < 15 mm in short axis, as well as truly non-measurable

lesions, which include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

9.1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. 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 when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For 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. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US). When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Tumor markers. Tumor biomarkers such as chromogranin A or urinary 5HIAA, cannot be the only method used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

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.

9.1.3 Response Criteria

9.1.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph node 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 with at least a 5 mm absolute increase in the sum of all lesions. The appearance of one or more new lesions* denotes disease progression.

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.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing for target lesions, the overall assessment must be UN unless there is new disease that would result in an overall assessment of PD. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

***Definition of New Lesion**: The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

9.1.3.2 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 subject to be considered in complete clinical response.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions* (new lesions must be > slice thickness) and/or unequivocal progression of existing non-target lesions.

Overall level of substantial worsening that merits discontinuation of therapy. A useful test that can be applied when assessing non-targets for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease.

Unknown (UN): Assessment of non-target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

***Definition of New Lesion**: The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

9.1.3.3 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 participant'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 for 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	

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

Note: Participants 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.

9.1.4 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 recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent 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.

9.1.5 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration from date of registration to time of objective disease progression per RECIST 1.1 criteria or death. Patients who come off study without documented progression of disease (or clinical progression) will be

followed and included in PFS analysis until documented progression, death from any cause, or initiation of a new anti cancer therapy.

9.1.6 **Response Review**

Tumor response will be evaluated at the study required time points by the DFHCC Tumormetrics Imaging Core (TIMC).

10. ADVERSE EVENT REPORTING REQUIREMENTS

10.1 Definitions

10.1.1 **Adverse Event (AE)**

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they are determined to be of clinical significance or require treatment or further diagnostic tests.

10.1.2 **Serious adverse event (SAE):**

A serious adverse event (SAE) is defined as any adverse event regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the study participant was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which had it occurred in a more severe form may have caused death.
- Requires or prolongs inpatient hospitalization (e.g., requires greater than 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect

- Other important medical event, as determined by the primary investigator. These events may not result in death or be life-threatening, or require hospitalization but may be considered to be SAE as they may require medical or surgical intervention to prevent one of the outcomes listed above. Some examples of this type of event are: allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency, drug abuse, or overdose with an associated serious event, or required intervention to prevent impairment/damage.

Events not considered to be SAEs are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite or palliative care

10.1.3 **Expectedness:**

AEs may be 'Expected' or 'Unexpected.'

10.1.3.1 **Expected AE:**

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the known adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agents.

10.1.3.2 **Unexpected adverse event**

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the known adverse event list, the Investigator's Brochure, the package inset, or the informed consent document as a potential risk.

10.1.4 **Attribution/Causality:**

Causality is a determination of reasonable possibility that the drug may have caused or contributed to an AE. It includes assessing temporal relationships dechallenge/rechallenge information, association (or lack of association) with underlying diseases and the presence (or absence) or a lack of one or more likely causes.

Attribution is the relationship between an AE or SAE and the study treatment. **The primary investigator will make final determination of attribution/causality.**

The primary investigator, sub-investigator or clinical research team will assign as follows:

- 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.
- Unknown- Based on the evidence available, causality cannot be ascribed.

10.2 Procedures for AE and SAE Recording and Reporting

Participating investigators and clinical research team will assess the occurrence and attribution of AEs and SAEs at all of the required evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record (source document) and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the 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 website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

10.3 Reporting Requirements

The study must be conducted in compliance with FDA regulations, Institutional safety reporting requirements, and DF/HCC reporting requirements of the principal investigator.

It is the responsibility of each participating investigator to report any serious adverse events to the primary study team and to the primary investigator, Jennifer Chan, MD, MPH.

The study sponsor and/or others will be notified as described below.

10.4 Reporting SAEs:

10.4.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Principal Investigator via email, phone or facsimile, to Sanofi Group and to the DF/HCC OHRS, using the DF/HCC SAE form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention need to be reported to DF/HCC IRB/Sanofi Group

- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial or when the event occurs within 30 days of the last study drug administration or if assessed as related at anytime therafter.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

All SAEs must be reported within 24 hours of learning of the occurrence to:

PI: Jennifer Chan, MD, MPH
jang@partners.org
Phone: 617-632-5370
Fax: 617-632-5370
and
Sanofi-Aventis
Sanofi Group Entity Pharmacovigilance Contact
USPVmailbox@sanofi-aventis.com
F: 908-203-7783

Follow-up information should be provided as soon as available, and will describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation. Results of any complementary exams performed to obtain a final diagnosis of an SAE (e.g., hospital discharge summary, autopsy results, operative reports) will be made available to Sanofi group upon request.

10.4.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator via Case Report Forms (eCRF).

10.5 Reporting to the Institutional Review Board (IRB)

In addition to notifying the primary investigator and Sanofi group, all DF/HCC sites will report SAEs (as noted above) directly to the DFCI Office for Human Research Studies (OHRS).

10.6 Reporting to Sanofi-aventis

The DF/HCC Overall Principal Investigator will report to Sanofi-Aventis, (regardless of the site of occurrence), any AE that is defined as serious and unexpected and is determined to be (possible, probable, or definitely) related to the study treatment.

Unexpected or SAEs associated with the use of the study treatment will be reported to Sanofi-aventis as soon as possible or within 7 calendar days after initial receipt of the information.

10.7 Reporting to Food and Drug Administration (FDA)

The DF/HCC Overall Principal Investigator, as holder of the IND, will be responsible for all communication with the FDA. The DF/HCC Overall Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800-FDA-0178) using Form FDA 3500A (Mandatory Reporting Form for investigational agents) or FDA Form 3500 (Voluntary Reporting Form for commercial agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

10.8 Reporting to Hospital Risk Management

Participating investigators or research team will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

10.9 Monitoring of Adverse Events and Period of Observation

All AEs (serious and non serious) and deaths that are encountered from first dose of study treatment, throughout the study, and within 30 days of the last study treatment should be:

- followed to their resolution,
- or participating investigator assesses them as stable,
- or participating investigator determines the event to be irreversible,
- or participant is lost to follow-up.

AEs will be recorded in the participant's medical record to facilitate source data verification. The presence and resolution of AEs and SAEs (with dates if available) should be documented on the appropriate case report form (eCRF).

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants will be advised to report any serious post-study event(s) that may reasonably be related to participation in this study.

Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

11. DATA AND SAFETY MONITORING

11.1 Data Reporting

11.1.1 Method

The QACT will collect, manage, and monitor data for this study.

11.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

11.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. The first review of the DSMC will occur after the first three patients enrolled have completed 1 cycle of therapy. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

Any significant safety issues or recommendations by the Data Safety Monitoring Committee will be submitted to Sanofi group.

11.3 Auditing

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

Data may be audited by QACT or if deemed necessary by the Overall Principal Investigator.

12. REGULATORY CONSIDERATIONS

12.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

12.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study.

The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure.

The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the research file a copy of the signed consent document will be scanned into medical record (LMR).

12.3 Ethics

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
    - Title 21 Part 50 – Protection of Human Subjects
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
    - Title 21 Part 56 – Institutional Review Boards
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
    - Title 21 Part 312 – Investigational New Drug Application
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

12.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

12.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The primary endpoint of this phase II study is to assess the progression free survival (PFS) of patients with advanced carcinoid tumors treated with Ziv-aflibercept. PFS is defined from the date of documented progression or death from any cause. Patients who come off treatment without documented progressive disease will be followed and included in PFS analysis until documented progression, death from any cause, or the initiation of a new anti cancer therapy.

Recent studies of targeted agents in neuroendocrine tumors suggest that while many of these agents are associated with low RECIST-defined response rates, they may be associated with significant progression free survival (PFS). In the registration studies of sunitinib and everolimus in pancreatic neuroendocrine patients, PFS durations more than doubled, while overall response rates were only 9% and 4% respectively.[10,11]

In this study of Ziv-aflibercept, we propose using PFS as the primary outcome measure. The RADIANT 2 study provides a reasonable estimate of PFS duration in a large cohort of carcinoid tumor patients treated with octreotide or octreotide plus an investigational agent (Pavel, Hainsworth, Baudin, et al ESMO congress, 2010). RADIANT 2 randomized 429 patients with a history of symptoms attributed to carcinoid syndrome and evidence of radiographic progression within 12 months of enrollment to receive everolimus plus octreotide LAR depot, or a placebo plus octreotide LAR depot. A significant PFS benefit in favor of everolimus was demonstrated based on investigator radiology review (12 vs. 8.6 months, $p < 0.01$). However, the primary endpoint of the study was based on adjudicated central review, and while this analysis also favored the everolimus arm over placebo, the predefined threshold for statistical significance was not met.

Investigator review will be used as the primary endpoint in the current study of Ziv-aflibercept in advanced carcinoid patients. Entry criteria will parallel those of the RADIANT 2 study, and will include a requirement for low or intermediate grade histology and for evidence of disease progression within 12 months of study entry. Concurrent treatment with octreotide will also be required. We assume that an

inactive agent will be associated with PFS of 8 months, and that an agent worthy of further investigation will be associated with PFS of 12 months or greater.

13.2 Sample Size/Accrual Rate

A sample size of 43 participants achieves 80% power to detect the difference between null hypothesis median PFS of 8 months and the alternative hypothesis median PFS of 12 months at a 0.05 significance level (alpha) using a one-sided test. This sample size also allows 90% power to detect the same effect size with 10% type one error using a one-sided test. The length of follow up is 2 years.

We expect an accrual rate of 1.5 patients per month.

13.3 Analysis of Secondary Endpoints

All patients treated with at least one dose of Ziv-aflibercept will be included in this data.

- Toxicity data, including laboratory values will be graded using CTCAE version 4.0.
- Response criteria will be assessed using RECIST 1.1 criteria.
- Values of chromogranin A and urinary 5HIAA will be analyzed for actual and/or relative (%) change from baseline. Correlation between changes from baseline may be explored graphically. The association of these markers and clinical outcomes of interest (e.g., time to progression) may be investigated.

13.4 Reporting and Exclusions

13.4.1 **Evaluation of PFS.** Patients who come off treatment without documented progressive disease will be followed and included in PFS analysis until documented progression, death from any cause, or the initiation of a new anti cancer therapy.

13.4.2 **Evaluation of toxicity.** All participants will be evaluable for toxicity after the administration of the first dose of Ziv-aflibercept.

13.4.3 **Evaluation of response.** All participants included in the study will be assessed for response to treatment. Each participant 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). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

14. PUBLICATION PLAN

Upon completion of this study and collection and analysis of all available data the results of this study will be submitted for publication within 3 years.

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16. APPENDICES

Appendix A:

Urine Protein/Creatinine Ratio

- Obtain at least 4 ml of a random urine sample
- Determine urine protein concentration (mg/dL) and urine creatinine concentration (mg/dL).
- Divide results of protein concentration by creatinine concentration= UPCR

Appendix B:

CORRELATIVE STUDIES

Consent for additional study blood samples will be requested in the informed consent document, but participation will be optional and eligible patients who do not consent to this portion of the study will still be able to proceed with study treatment. The purpose of obtaining these samples is to explore potential biomarkers that correlate with Ziv-aflibercept treatment outcomes. Samples will be analyzed after the completion of the clinical portion of this study in order to better understand biologic correlates of the clinical activity of Ziv-aflibercept in this population. The analysis will be performed at a laboratory designated by the principal investigator. All samples will be stored and labeled according to directions below. All samples will be destroyed after a maximum of 10 years.

The analysis of results will not be made available to the individual study participant or the treating physician; however, group results from this trial may be published when the final data is available.

Study samples will be drawn by an experienced phlebotomist or a research nurse during the course of normally scheduled blood draws obtained as part of the treatment study. Blood samples may be drawn either peripherally or via a central line. Each site will be responsible for ordering their own laboratory supplies and shipping materials for the specimens. Shipping costs and supplies will be covered by the protocol budget. Specimens will be stored at each DF/HCC site.

Specific instructions for study blood samples are described below:

Whole Blood Samples:

A single tube of whole venous blood will be collected at baseline and will be stored for future studies of biomarkers that may prove useful at that time. Venous blood will be collected into one 6 ml purple-top EDTA tube. After collection of the sample, the tube should be gently inverted to ensure mixing with the anticoagulant. Whole blood should be transferred from EDTA tube into labeled cryotubes and frozen at –20C.

All cryovials will be labeled as follows:

1. Protocol Number: 12-456
2. Unique subject identifier (initials of the patient and subject study #)
3. Collection date
4. Tube # (there should be approximately 2 cryovials; please note contents, i.e Whole Blood)

Plasma Samples:

Plasma samples will be drawn at the following time points:

- Prior to initiation of therapy (may be done on C1D1 prior to administration of study drug)
- Day 1 of each subsequent treatment cycle
- End of study

Approximately 5-7 ml of blood for plasma-based studies will be collected in EDTA (purple top) tubes. Plasma samples should be processed by inverting the tube several times to assure complete mixing of anticoagulant (EDTA) and immediately centrifuged in a clinical centrifuge at 3,000 r.p.m. for 10 minutes at room temperature. Plasma should be aspirated without disturbing cells, aliquoted in 3 cryogenic vials, and frozen at –80C.

All cryovials will be labeled as follows:

1. Protocol Number: 12-456
2. Unique subject identifier (initials of patient and study subject #)
3. Collection date
4. Tube # (there should be 3 cryovials)/ please note contents (plasma)

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Appendix C:
12-456 : Home Blood Pressure Monitoring Diary and Instructions

Name_____ MRN#_____
Cycle_____ Doctors office phone number:_____

Instructions:

1. Blood Pressure readings have two numbers. The first number is the pressure in your blood vessels during a heart beat (systolic), and the second number is the pressure in the vessels when the heart rests in between beats (diastolic). These numbers are written with a slash in between them (*for example, 110/85*).

2. Record the date, then record your blood pressure **ONCE daily** using a home blood pressure monitor. Record your blood pressure at approximately the same time of day (while you are relaxed and sitting and after you have rested for at least 5 minutes). If you take your blood pressure at other times of the day, please record under "Other readings".

3. A normal blood pressure is usually considered to be 120/80 mmHg. **If your systolic pressure is greater than 150 or your diastolic blood pressure is greater than 90** (150/90 or greater →, try to relax, wait one hour, and recheck. If the second reading is greater than or equal to 150/90 please contact your doctor's office for instructions.

Date	AM readings	PM readings	Comments or "other readings" (include time and date)
	/	/	****Please bring this form to every clinic visit or appointment**.
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	/	/	
	/	/	
	/	/	
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Patient's Signature: _____ Date: _____

Study Team Signature_____ Date returned: _____

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