SUMMARY OF CHANGES

Date: August 21, 2017

Document: NCI Protocol #8628, PhII-107: "A Randomized Phase II Study of Sequential Biotherapy with Aflibercept and High Dose IL-2 versus High Dose IL-2 alone in Patients with Inoperable Stage III or Stage IV Melanoma: Efficacy and Biomarker Study."

Note: The following is a Summary of Changes between the 12.31.15 and 8.21.17 version of the protocol

Section	**Description of Change (v. 12.31.15 and v. 8.21.17)**
Face page	Added August 21, 2017 to the list of protocol versions and updated the footer. Updated the principal investigator and other participating investigators.

NCI Protocol #: 8628

Local Protocol #: PhII-107

TITLE: A Randomized Phase II Study of Sequential Biotherapy with Aflibercept and High Dose IL-2 versus High Dose IL-2 alone in Patients with Inoperable Stage III or Stage IV Melanoma: Efficacy and Biomarker Study

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NCI Supplied Agent: Aflibercept (NSC 724770)

Commercial Agent: Aldesleukin (Interleukin-2)

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June 14, 2010	Intial Protocol
August 2, 2010	Response to Consensus Review
August 18, 2010	Response to Follow Up Review
December 8, 2010	Amendment
December 20, 2010	Address recommendations, study calendar
June 16, 2011	Update investigator on title page
July 18, 2011	Update investigator on title page
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May 11, 2012	Amendment
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January 23, 2015	Amendment – disapproved
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August 21, 2017	Amendment

SCHEMA

This is a randomized phase II study of sequential biotherapy with aflibercept and high dose interleukin-2 (IL-2) versus high dose IL-2 alone in patients with advanced inoperable stage III or stage IV melanoma.

Arm A: Combination of Aflibercept and IL-2.
The planned treatment consists of 3 courses of combination aflibercept and high dose IL-2 followed by maintenance aflibercept monotherapy. Response assessment will occur at the end of each course of combination therapy and patients without evidence of disease progression (RECIST v.1.1) or limiting toxicities will be offered additional courses of treatment (or maintenance aflibercept therapy).

Arm B: High dose IL-2 alone
The planned treatment consists of 3 courses high dose IL-2. Response assessment will occur at the end of each course of therapy and patients without evidence of disease progression (RECIST v.1.1) or limiting toxicities will be offered additional courses of treatment of high dose IL-2 for a maximum of 3 courses (6 cycles).

Arm A will be conducted in 2 phases: Combination and Aflibercept Monotherapy. The combination phase will consist of courses 1, 2 and 3 during which aflibercept will be administered at 3mg/kg. For the Aflibercept Monotherapy phase, aflibercept will be administered at 4 mg/kg.

I. Combination Phase (Arm A):

	Course 1 (Arm A)									
	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10
Aflibercept 3 mg/kg IV	X		X		X		X		X	
HD IL-2 600,000 U/kg/dose IV Q8h x 5 days (max 14 doses)			X		X					
Response Assessment										X

	Course 2 (Arm A)								Course 3(Arm A)							
	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8
Aflibercept 3 mg/kg IV	X		X		X		X		X		X		X		X	
HD IL-2 600,000 U/kg/dose IV Q8h x 5 days (max 14 doses)	X		X						X		X					
Response Assessment								X								X

II. Aflibercept Monotherapy/Maintenance Phase for Arm A:

Following response assessment after course 3 of combination therapy and after resolution of all toxicities to ≤ grade 1 (CTCAE v.4), aflibercept monotherapy will be initiated to be administered at 4 mg/kg IV on Day 1of each 14-day cycle. In this case, blood pressure monitoring should be done weekly for the first 3 weeks of the maintenance phase to ensure tolerance of the higher aflibercept dose. However, if the aflibercept dose had to be reduced during the combination phase due to aflibercept-related toxicities, then that reduced dose will be used for maintenance therapy. No need for weekly monitoring of blood pressure, if the reduced dose has already been demonstrated to be tolerable.

Primary Objective: Test the hypothesis that combination biotherapy with aflibercept and HD IL-2 will improve the progression-free survival compared to HD IL-2 alone.

Secondary Objectives: (1) Evaluate the response rate (CR+PR) of aflibercept and HD IL-2 as assessed by RECIST criteria version 1.1 and compare to HD IL-2 alone. (2) Evaluate the toxicities and tolerance of combination biotherapy with aflibercept and HD IL-2 and maintenance aflibercept alone in this patient population and compare to HD-IL2 alone. (3) Test the hypotheses related to the laboratory correlative studies. (4) Evaluate the overall survival of patients treated on Arm A and B.

The primary endpoint is progression-free survival. The accrual goal is 105 patients, 70 on Arm A, and 35 on Arm B.

Definitions:

1. A **cycle of IL-2**: eligible patients receive high-dose IL-2 at 600,000 IU/kg IV every 8 hours for up to 14 doses. This constitutes one cycle of IL-2.
2. A **cycle of Aflibercept**: eligible patients receive aflibercept at 3 mg/kg (combination phase) or 4 mg/kg (maintenance phase) IV every 2 weeks. This constitutes one cycle of aflibercept.

3. The **combination phase (Arm A)**: during this phase, IL-2 and aflibercept will be given concurrently. It consists of 3 courses of combination therapy.
    a. Each course consists of 2 cycles of IL-2 as follows: high-dose IL-2 at 600,000 IU/kg is given IV every 8 hours for up to 14 doses (one cycle), followed by a rest period of 1-2 weeks and readmission for a second high dose IL-2 cycle for up to 14 doses (2^{nd} cycle).
    b. In addition, aflibercept will be given concurrently at 3 mg/kg IV every 2 weeks, but in course 1 only aflibercept will start 2 weeks prior to IL-2. Therefore, course 1 will consist of 5 cycles of aflibercept, while courses 2 and 3 will consist of 4 cycles of aflibercept each.
    c. Based on the occurrence of treatment-related toxicities and requirements for dose adjustments or delays, a patient may or may not receive the full planned treatment, but response assessment will continue to be carried out at the end of each course.
4. The **maintenance phase (Arm A)**: only aflibercept monotherapy will be given during this phase for Arm A patients at 4 mg/kg IV every 2 weeks. Response assessment will be carried out every 12 weeks (-/+1 week) for both arms (for arm A patients, approximately every 6 cycles of aflibercept) for the first 2 years, then every 6 months (-/+ 2 weeks) for years 3-5, then yearly (-/+ 4 weeks) afterwards.

For arm B, patients will receive HD IL-2 alone following the institutional standard of care guidelines. Patients will receive a maximum of 3 courses (6 cycles; 1 course of IL_2 in arm B = 2 cycles of IL-2). Response assessment will be carried out at the end of each course. In the absence of disease progression by RECIST v.1.1, patients will be offered additional courses of therapy for a maximum of 3 courses (6 cycles).

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1. OBJECTIVES

1.1. Primary Objectives

- Test the hypothesis that combination biotherapy with aflibercept and HD IL-2 will

improve the progression-free survival compared to HD IL-2 alone.

1.2. Secondary Objectives

- Evaluate the response rate (CR+PR) of aflibercept and HD IL-2 as assessed by RECIST criteria version 1.1 and compare to results of HD IL-2 alone.

- Evaluate the toxicities and tolerance of combination biotherapy with aflibercept and HD IL-2 and maintenance aflibercept alone in this patient population and compare to HD IL-2 alone.

- Test the hypotheses related to the laboratory correlative studies.

- Evaluate the overall survival of patients treated with aflibercept and HD IL-2 and HD IL-2 alone.

2. BACKGROUND

2.1. Metastatic Melanoma

Annually, about 8,000 patients are found to have metastatic melanoma presenting as a recurrence of an earlier primary melanoma, and this number closely approximates the annual number of deaths from this disease [1]. This statistic illustrates the lack of progress that has been made in the treatment of stage IV melanoma over the last several decades. Therapeutic approaches that have been studied in metastatic melanoma include chemotherapy, biochemotherapy, nonspecific immune adjuvants, cancer-specific vaccines, cytokines, monoclonal antibodies, and specific immunostimulants [1]. Chemotherapy with single agent dacarbazine is the only US-FDA approved chemotherapy agent for metastatic melanoma. Immunological approaches have yielded the only new US-FDA approved agent for metastatic disease in 30 years, high-dose bolus interleukin-2 (IL-2), based on prolonged durable responses in some patients with metastatic melanoma [2]. Participation in clinical trials is presently the best strategy to maximize therapeutic options and to access novel drugs in clinical development. Many novel therapeutic approaches are currently undergoing active clinical investigation and emerging data are promising from approaches targeting angiogenesis, or targeting groups of patients with specific activating mutations that are driving malignant proliferation such as the V600E BRAF mutation and mutations and amplifications in the receptor tyrosine kinase c-kit. This is in addition to immunotherapy with anti-CTLA4 monoclonal antibodies. Although promising, clinical benefits from current investigational agents appear to be of either limited duration and/or confined to small groups of patients. Therefore, there continues to be an urgent need for new therapeutic strategies building upon promising clinical activity data and solid preclinical rationale.

2.2. Aflibercept (VEGF Trap, AVE0005)

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). 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). Aflibercept drug product is formulated as a sterile liquid for intravenous (IV) administration [3].

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 aflibercept to its ligands in vivo is expected to block tumor angiogenesis and vascular permeability.

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, aflibercept inhibited ascites formation and reduced tumor burden.

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. The most common adverse events reported for aflibercept monotherapy include: hypertension, proteinuria, epistaxis, dysphonia, pain (including abdominal pain and back pain), asthenia/fatigue, nausea, vomiting, headache, constipation, myalgia, arthralgia, dyspnea, decreased appetite, and diarrhea.

Target pharmacological exposure has been reached at doses ≥2 mg/kg IV given every 2 weeks. Free aflibercept levels have remained in excess of bound 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 aflibercept monotherapy and with aflibercept administered in combination with cytotoxic chemotherapy. Phase 1 studies, as both single agent and combination chemotherapy, are ongoing. Phase 2 studies of aflibercept, either alone or in combination with standard cytotoxic agents, are ongoing in a variety of oncologic indications. Phase 3 combination studies are ongoing in the following indications: lung cancer, colorectal cancer, pancreatic cancer, and prostate cancer [3].

2.2.1. Animal Toxicology

The toxicity profile of 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, 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. Aflibercept administration also resulted in a decrease in sperm motility and increased incidence of abnormal spermatozoa morphology. Most 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, 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.

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) 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).

2.2.2. Mechanism of Action

VEGF is a molecule produced by tissues to stimulate angiogenesis. VEGF production by tumors is required for vascularization and thus, the survival and growth of tumors. VEGF protein that is not internalized through its VEGF receptor mediated signaling reaches the circulation where it is cleared rapidly. The VEGF Trap, a long-acting inhibitor of VEGF signaling, potently binds and inactivates VEGF, thus blocking tumor angiogenesis and growth in both animal models of cancer and in humans with a variety of cancers.

2.2.3. Pharmacokinetics

Free aflibercept is cleared by 2 mechanisms in humans: (1) a fast clearance by binding systemic VEGF to form bound aflibercept, and (2) a slower pathway where the free aflibercept is eliminated by other biological mechanisms, perhaps analogous to the clearance of free antibodies (proteins). The results in humans are

similar to observations in animal studies.

The clinical kinetics of aflibercept were characterized by a low volume of distribution approaching blood volume and a low clearance decreasing with dose in the dose range 0.3 to
2 mg/kg, then stable at higher doses.

Target pharmacological exposure has been reached at 0.8 mg/kg SC given weekly or ≥2 mg/kg IV doses given every 2 weeks. Free aflibercept levels have remained in excess of bound aflibercept levels throughout the dosing intervals at these doses.

Following IV administration, the pharmacokinetics of free aflibercept were not linear following administration of <2 mg/kg doses, but became linear between the 2 and 7 mg/kg dose levels. The
pharmacokinetics of free aflibercept were characterized by high fluctuation and essentially no accumulation when given every 2 weeks. The concentrations of bound aflibercept increased between the 0.3 and 2 mg/kg dose levels, and then plateaued between the 2 and 7 mg/kg dose levels, suggesting that free aflibercept was available in sufficient amount to bind all endogenous VEGF in this higher dose range.

Free and bound aflibercept concentrations determined in combination studies are in the same order of magnitude of those observed in the monotherapy study TED6115, suggesting that cytotoxic combinations (FOLFOX 4, irinotecan, 5-FU, docetaxel, and gemcitabine) have no influence on the PK of aflibercept. Anti-aflibercept antibodies have been reported using ELISA methods. These findings are not unexpected, as aflibercept is a recombinant protein product. The immunogenicity testing with present methods showed that less than 1% of patients evaluated developed anti-aflibercept antibodies. Further assay development is ongoing and the implications and understanding of anti-aflibercept antibodies is under evaluation.

2.2.3.1. Pharmacokinetic/Pharmacodynamic Relationships

Preclinically, circulating levels of VEGF Trap complex appear to be good biomarkers of efficacy. VEGF is normally cleared rapidly and does not accumulate, but binding to VEGF Trap creates an inactive VEGF**:**VEGF Trap complex with a longer half-life that accumulates to detectable levels. Because of the high affinity of VEGF Trap for VEGF, free VEGF Trap is rapidly converted to the bound form unless VEGF Trap levels exceed the amount of VEGF synthesized over the dosing interval. At high doses of VEGF Trap, essentially all VEGF is trapped, VEGF**:**VEGF Trap complex formation is saturated, and free VEGF Trap accumulates. Antitumor efficacy in animal xenograft models was observed at VEGF Trap doses that resulted in saturation of steady-state VEGF**:**VEGF Trap complex (bound VEGF Trap) plasma levels and an excess of free VEGF Trap over the

complex concentrations, as shown in Figure 2 of the Investigator's Brochure [3].

2.2.4. Clinical Experience

To date, aflibercept has been administered to 76 healthy subjects and approximately 2000 patients with advanced solid malignancies in clinical oncology trials. In company-sponsored trials, doses have been administered up to 800 μg/kg twice weekly SC and 7 mg/kg IV every 2 weeks, and 9 mg/kg IV every 3 weeks across 13 Phase 1 clinical trials (11 oncology trials), four Phase 2 single agent, two Phase 2 combination trials, and four Phase 3 combination trials. Details of Phase 1 trials in healthy subjects are presented in Table 36 of IDB. Details of the company sponsored clinical oncology trials are presented in Table 37 of IDB; SAEs in these trials are summarized in Table 39 of ID, Table 40 of IDB, Table 41 of IDB, and Table 42 of ID.

2.2.4.1. Efficacy

In the single agent Phase 1 study of SC aflibercept, 2 patients, 1 with heavily pretreated bronchoalveolar carcinoma and another with medullary thyroid cancer, improved either subjectively and/or radiologically at a dose of 800 μg/kg with prolonged disease stabilization of over 2 years.

In the Phase 1 studies of IV single agent aflibercept (TED6115 and TED6116), 3 patients have had RECIST-defined partial tumor responses: 1 patient with metastatic malignant thymoma treated at the 3 mg/kg dose level, and 2 patients with ovarian cancer treated at the 7 mg/kg dose level. Two patients with renal cell cancer, treated at the 1 mg/kg and 2 mg/kg dose levels, respectively, have had prolonged (exceeding one year) stable disease (SD).

Single agent Phase 2 studies in previously treated patients (2 or more lines of chemotherapy treatment) have evaluated aflibercept administered IV every 2 weeks in ovarian and lung cancer (ARD6122, ARD6123) with response rate as the primary endpoint. In ARD6123, a single agent, single arm study of aflibercept at 4 mg/kg in advanced, heavily pretreated non-squamous nonsmall cell lung cancer (NSCLC), an Investigator-reported overall response rate (ORR) of 2% was observed, along with a median progression free survival (PFS) of approximately 12 weeks, and stable disease (SD) for ≥60 days of approximately 30%. The median overall survival (OS) was approximately 6 months. In ARD6122, a randomized, double-blind study of aflibercept at 2 mg/kg or 4 mg/kg in advanced ovarian cancer, the Investigator-reported ORR was 3.8% in the 2 mg/kg arm and 7.3% in the 4 mg/kg arm; the median PFS in both arms was approximately 18 weeks, and SD for ≥60 days of approximately 45% and 37% in the 2 mg/kg and 4 mg/kg arms, respectively. The median OS was approximately

55 weeks in the 2 mg/kg arm and 50 weeks in the 4 mg/kg arm.

Additionally, single agent Phase 2 studies have explored the efficacy of aflibercept in prolonging the time to repeat paracentesis in advanced ovarian cancer patients with symptomatic malignant ascites (SMA). Study ARD6772 explored 4 mg/kg IV every 2 weeks, and showed at least a doubling of the primary endpoint (time to repeat paracentesis compared to baseline) for 62% of the patients. Study EFC6125, a randomized, double blind study of aflibercept 4 mg/kg IV every 2 weeks versus placebo, in a similar patient population, is still ongoing.

In the combination Phase 1 studies, radiological tumor responses per RECIST criteria have been observed across different tumor types and aflibercept doses.

2.2.4.2. Phase II monotherapy study in advanced melanoma

A phase II study of aflibercept in patients with inoperable stage III or IV melanoma who had received no prior chemotherapy or hormonal therapy has recently completed accrual. A 2-stage design was adopted focusing upon response rate (RECIST) and 4-month PFS rate. First stage accrual of 21 patients was specified, and accrual continued to a total of 41 patients due to an adequate 4 month PFSR. Aflibercept was given at 4 mg/kg IV every 2 weeks. Response was assessed every 8 weeks. Forty one patients (26 male, 15 female), age 23-83 (median 57) have been enrolled. All had AJCC stage IV melanoma (2N3, 3M1a, 8M1b, 28M1c). Karnofsky PS: 100 (19), 90 (14) or 80 (8). Ten patients had primary ocular melanoma, 28 cutaneous and 3 unknown primary site. A median of 4 cycles have been administered (range 1-23). Grade 3/4 toxicities included cerebral ischemia (1 patient; 2%), confusion (1; 2%), thrombocytopenia (1; 2%), hypertension (8; 20%), hypotension (1; 2%), left ventricular diastolic dysfunction (1; 2%), fatigue (1; 2%), proteinuria (4; 10%), extraocular muscle paresis (1; 2%), renal failure (1; 2%), back pain (1; 2%), headache (1; 2%), osteonecrosis of mandibular bone in a patient with a history of external beam radiation therapy. Overall, one patient (cutaneous, M1c) had a confirmed partial response (potential CR; duration of PFS = 293+ days). Twenty patients have had stable disease (10 ongoing, 10 have progressed). Four patients were taken off study prior to response evaluation for toxicity (3) or treatment refusal (1). One patient is currently disease free who was not evaluable for response (previous surgery and radiofrequency ablation of measurable disease site). Thirteen patients had progression at first assessment point. Thus far 16 patients (excluding the non-evaluable NED patient) have had at least 4 months of PFS. Eight additional patients are still on treatment, but have not reached the 4 month PFS milestone.

These results have lead the investigators to conclude that aflibercept has a

promising clinical activity in metastatic melanoma of cutaneous or ocular origin. The final conclusions on the activity of aflibercept as single agent in metastatic melanoma require additional follow up (4 months after the last patient has started treatment). These data however, provide strong rationale for moving forward with further development of aflibercept in combination therapy with agents that are known to be active in melanoma [4].

2.2.5. Safety Considerations

Phase 1, 2, and 3 oncology studies are ongoing, as both single agent and combination trials.

In healthy subjects, administration of a single dose, or up to 2 doses of 1, 2, or 4 mg/kg of aflibercept by IV infusion, or 2 mg/kg by SC route, was considered safe and showed an acceptable tolerability. The most frequently reported treatment emergent non-serious AEs included headache, dysphonia, epistaxis, acneiform dermatitis, nasopharyngitis, arthralgia, diarrhea, ALT increase, and nausea/dyspepsia. No serious adverse events (SAEs) were reported in healthy subjects.

All grade treatment emergent adverse events (TEAEs) commonly reported across single agent oncology trials, regardless of relationship to study drug, include hypertension, proteinuria, epistaxis, dysphonia, pain (including abdominal pain, musculoskeletal pain, and back pain), asthenia/fatigue, constipation, nausea, vomiting, diarrhea, dizziness, headache, cough, dyspnea, decreased appetite, peripheral edema, and pyrexia. Serious and less commonly reported events include thrombotic microangiopathy, cardiac failure, gastrointestinal hemorrhage, intestinal perforation, hemoptysis, tracheoesophageal fistula, enterocutaneous fistula, reversible posterior leukoencephalopathy syndrome (RPLS), intracerebral hemorrhage, cerebral ischemia, deep vein thrombosis and pulmonary embolism. Although these AEs may be drug related, an association with the underlying disease and the heavily pretreated patient population studied cannot be ruled out at this stage of development.

All grade TEAEs commonly reported across trials exploring aflibercept in combination with other anticancer drugs are similar to the single agent drug safety profile but also reflect common toxicities associated with the drugs used in these combination regimens. Some anticancer drugs being explored in Phase 1 combination studies include: docetaxel, gemcitabine, erlotinib, irinotecan, oxaliplatin, cisplatin, and fluorouracil. Adverse events commonly reported in the combination trials include hypertension, proteinuria, epistaxis, dysphonia, pain (including abdominal pain, musculoskeletal pain, and back pain), asthenia/fatigue, nausea, vomiting, headache, constipation, dyspnea, decreased appetite, diarrhea, and also include neuropathy, stomatitis and mucosal inflammation, electrolyte changes (including hypomagnesemia), and alopecia. Hematological abnormalities commonly reported in the combination trials include neutropenia, anemia, and

thrombocytopenia.

For more details on AEs associated with Aflibercept, please refer to the current version of the IDB [3].

2.3. High Dose Interleukin-2

IL-2 plays a central role in immune regulation as it affects the survival of key cells of the immune system that are responsible for the antitumor cytotoxicity of T-lymphocytes and natural-killer (NK) cells, and it has a cofactor role in the activation of B cells and macrophages [5]**.** The administration of IL-2 at high bolus IV doses once every eight hours was a regimen developed by the National Cancer Institute (NCI) based on animal models indicating that antitumor activity with this agent was dose-dependent [6][6][6][6][6][7]. Initial studies with HDB IL-2 utilized doses of 600,000-720,000 units/kg every 8 hours from days 1-5 (cycle 1) and days 15-19 (cycle 2) with a maximum of 14 doses per cycle or 28 doses per course (1 course = 2 cycles). Responding or stable patients were offered a second course of therapy 8-12 weeks later. IL-2 was administered either as a single agent or in combination with immunologically active cells, so-called adoptive immunotherapy. The latter technique utilized two types of immune cells: the lymphokine- activated-killer (LAK) cells and the tumor infiltrating lymphocytes (TIL).

Eight clinical trials conducted between 1985 and 1993 and using the HDB IL-2 regimen described above, with or without LAK cells, were reviewed in a retrospective analysis. These trials had an enrollment of 270 patients with advanced metastatic melanoma [7-9][7-9][7-9][7-9][7-9][8-10]. In those studies that involved the concurrent administration of LAK cells, these cells were obtained using leukapheresis from patients during the rebound lymphocytosis that occurs following treatment and cessation of bolus IL-2 (days 8 to 12). LAK cells were then cultured in IL-2 for 3 to 4 days. These generated LAK cells were reinfused with IL-2 during the second cycle of IL-2 administration. The retrospective analysis of these trials with a follow-up through December 1998 along with a more recent update demonstrated an objective response rate of 16% with durable responses in 4% of patients [2, 10][2, 10][2, 10][2, 10][2, 10][3, 11]. The median response duration was 8.9 months (range 4 to 106+ months). Twenty eight percent of the responding patients, including 59% of those patients who had achieved a complete response, have remained progression free at a median follow-up of 62 months. Furthermore, no patient who had responses longer than 30 months has relapsed, suggesting the possibility that these patients may be “cured”. The frequency of the responses was similar in patients with visceral metastases and/or large tumor burdens, but the responses were less in patients with poor performance status or those who had received prior systemic therapy. Based on these data, HDB IL-2 received approval by the US-FDA for the treatment of metastatic melanoma [11][11][11][11][11][12]. In addition to being logistically challenging, randomized studies have not shown superiority for IL-2 administered with LAK cells versus therapy with HD IL-2 alone [12][12][12][12][12][13]. Furthermore, a randomized phase III trial of CD8+ TIL given in combination with rIL-2 in metastatic renal cell carcinoma has been negative [13][13][13][13][13][14].

2.3.1. Baseline Serum VEGF as a Predictor for Non-Response to HD IL-2

Sabatino et al. have reported the results of proteomic analysis of the serum of patients (predominantly with metastatic melanoma; N=100, including 48 with melanoma and 11 with RCCA) who were treated with high-dose IL-2, using a customized, multiplex antibody targeted protein array platform to survey expression of soluble factors associated with tumor immunobiology [14]. Soluble factors associated with clinical responses were analyzed using a multivariate permutation test and survival outcomes were determined using Kaplan-Meier and log-rank tests. The customized Pierce SearchLight Proteome Arrays^{R}, (Boston, MA) measured 16 proteins per well in standard 96 well plates spotted with different monoclonal antibodies. Sandwich ELISA was utilized to generate chemiluminescence signals for calculation of the levels of each analyte. Sixty patients were enrolled in this study. One patient did not complete staging scans and could not be included in response determination leaving 59 patients for complete analysis. Nineteen patients exhibited an objective response to IL-2 therapy; 18 of 48 melanoma patients (5 complete and 13 partial) and 1 of 11 RCC patients (1 partial) responded.

A training set of 10 patients identified 68 of 110 analytes as potentially relevant and an independent validation set of 49 patients was then analyzed. Vascular endothelial growth factor (VEGF) and fibronectin were identified as independent predictors of non-response to HD IL-2. In particular, high levels of these proteins correlated with lack of clinical response and decreased overall survival. Combining training and validation analyses identified only VEGF as a predictor of response to IL-2 therapy, although fibronectin maintained statistical significance after combining the data sets suggesting a potential role as an independent predictive biomarker. Patients with serum VEGF levels greater than 125 pg/ml or fibronectin levels greater than 8 x 106 pg/ml did not respond to IL-2 therapy and elevated levels of these proteins were also associated with a significantly worse overall survival. The VEGF family plays a critical role in mediating angiogenesis, lymphangiogenesis, and vasculogenesis and has an impact on host innate and adaptive immunity [15, 16]. The role of excess VEGF on tumor angiogenesis is well documented and recently high circulating serum levels of VEGF were associated with poor prognosis in patients with metastatic melanoma [17]. VEGF has been shown to block maturation of dendritic cells and inhibit effective priming of T cell responses [18, 19]. These data support an important role for VEGF in the progression of cancer and evasion of anti-tumor immunity. A therapeutic strategy designed to deplete high serum VEGF levels prior to HD IL-2 administration may reverse the negative impact of high serum VEGF on dendritic cell maturation and T cell priming allowing more effective antitumor T cell cytotoxicity induced by HD IL-2.

2.3.2. Studies Testing Bevacizumab in Combination with HD IL-2

The safety of the combination of VEGF Trap and High dose IL-2 can be expected based on studies involving bevacizumab and IL-2. These include an ongoing phase II study of bevacizumab and HD IL-2 in patients with metastatic renal cell carcinoma (A Cytokine Working Group Study). In this study, patients receive bevacizumab IV over 30-90 minutes on days -13, 1, 15, 29, 43, 57, and 71 during course 1 and on days 1, 15, 29, 43, 57, and 71 during courses 2 and 3. Patients also receive high-dose interleukin-2 every 8 hours on days 1-5 and 15-19. Treatment is repeated every 84 days for up to 3 courses in the absence of disease progression or unacceptable toxicity. Results of the first 15 of a planned 60 patients were reported in the ASCO 2007 Annual Meeting (Ernstoff et al.; Abstract 15524) demonstrated that HD IL-2 and bevacizumab can be given safely. This study has been updated for ASCO 2010 revealing a consistent safety profile (Dandamudi UB, et al. Abstract #4530). Another study presented in ASCO 2007 (Gracia et al.; Abstract 5103), is a phase II trial of low-dose IL-2 (250,000 U/kg/d SC D1-5 during week 1 and 125,000 U/kg/d SC D1-5 during weeks 2-6, followed by a 2 week break) and bevacizumab (10mg/kg was administered IV every 2 weeks starting on day -14) in patients with metastatic renal cell carcinoma.

2.4. Rationale

The VEGF family plays a critical role in mediating angiogenesis, lymphangiogenesis, and vasculogenesis and has an impact on host innate and adaptive immunity [15, 16]. The role of excess VEGF on tumor angiogenesis is well documented and recently high circulating serum levels of VEGF were associated with poor prognosis in patients with metastatic melanoma [17]. VEGF has been shown to block maturation of dendritic cells and inhibit effective priming of T cell responses [18, 19]. These data support an important role for VEGF in the progression of cancer and evasion of anti-tumor immunity. In addition, recent studies have identified baseline serum VEGF as a marker of immune resistance that is predictive for non-response to HD IL-2 [14]. A therapeutic strategy designed to deplete high serum VEGF levels prior to HD IL-2 administration may reverse the negative impact of high serum VEGF on dendritic cell maturation and T cell priming allowing more effective antitumor T cell cytotoxicity induced by HD IL-2. in addition, our data with aflibercept as monotherapy has shown promising clinical activity in advanced metastatic melanoma with an acceptable safety profile [4].

We hypothesize that sequential biotherapy with aflibercept, as a high-affinity soluble VEGF receptor and potent angiogenesis inhibitor, and HD IL-2 will lead to improved anti-tumor immunity compared to HD IL-2 alone. This should translate into improved anti-tumor clinical efficacy compared to either single agent.

2.4.1. Rationale for the doses selected in the combination and montherapy phases

The study will be conducted in 2 phases for arm A patients: Combination and Aflibercept Monotherapy. The combination phase will consist of courses 1, 2 and 3 during which aflibercept will be administered at 3mg/kg. For the Aflibercept Monotherapy Phase aflibercept will be administered at 4 mg/kg.

Our primary hypothesis is that the reduction or depletion of high serum VEGF levels prior to HD IL-2 administration would reverse immune resistance and the negative impact of high serum VEGF on dendritic cell maturation and T cell priming allowing more effective antitumor T cell cytotoxicity induced by HD IL-2. It will ultimately lead to a significant improvement in clinical outcome.

For aflibercept, target pharmacological exposure has been reached at doses ≥2 mg/kg IV given every 2 weeks. Free aflibercept levels have remained in excess of bound aflibercept levels throughout the dosing intervals at this, or higher doses. In addition, the concentrations of bound aflibercept were to increase between the 0.3 and 2 mg/kg dose levels, and then plateau between the 2 and 7 mg/kg dose levels, suggesting that free aflibercept was available in sufficient amount to bind all endogenous VEGF in this higher dose range.

Our experience with Aflibercept monotherapy at 4 mg/kg in a phase II study conducted in melanoma has shown that approximately 16 (out of 41) patients that had an aflibercept dose delay due to toxicity in the first 6 months of therapy. There were also 18 patients (of the 41) who had grade 3 or 4 toxicity attributed (possibly, probable or definite) to VEGF-trap. All patients who had grade 3-4 had their first grade 3-4 within the first 6 months. Therefore, we expect that at 4 mg/kg a significant group of patients may have the HD IL-2 treatment delayed in the combination phase.

3. PATIENT SELECTION

3.1. Eligibility Criteria

3.1.1. Patients must have histologically or cytologically confirmed metastatic melanoma (includes AJCC stage IV or advanced/inoperable stage III. Also includes patients with a history of lower stage melanoma and subsequent recurrent metastatic disease that is either locally/regionally advanced/inoperable disease or distant metastases).

3.1.2. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as >10 mm with CT scan or clinically (must be measurable with calipers) according to RECIST version 1.1 [20]. See Section 10 for the evaluation of measurable disease.

3.1.3. Patients must be free of brain metastasis by contrast-enhanced CT/MRI scans within 4 weeks prior to enrollment. If known to have prior brain metastases, must not have evidence of active brain disease after definitive therapy (surgery, radiation therapy or stereotactic radiosurgery) on two successive MRI evaluations at least 3 months apart (one of which is ≤ 4 weeks prior to starting the study drugs).

3.1.4. A patient may be treatment naïve. However, up to two prior regimens for metastatic melanoma are allowed. Prior adjuvant IFN-α is allowed. No prior therapy with bevacizumab, aflibercept or interleukin-2 (IL-2).

Patients must not have received systemic therapy or radiotherapy within the preceding 4 weeks. Patients must have recovered from adverse events due to agents administered more than 4 weeks earlier.

Patients must be at least 4 weeks from major surgery and have fully recovered from any effects of surgery, and be free of significant detectable infection.

For patients who have received prior anti-CTLA4 monoclonal antibody therapy (ipilimumab or tremelimumab), there is a risk of bowel perforation with IL-2 therapy. Therefore, for these patients if they have a history of colitis or diarrhea during anti-CTLA4 monoclonal antibody therapy, they should have a formal evaluation by a gastroenterologist and a colonoscopy should be considered to demonstrate the absence of active bowel inflammation before initiating IL-2 therapy on this protocol.

3.1.5. Age >16 years.

Because VEGF Trap interferes with growth plate maturation in animals, this agent may be inappropriate for use in patients <16 years of age. For this reason and because no dosing or adverse event data are available on the use of VEGF Trap in children, patients <16 years of age are excluded from this study but may be eligible for future pediatric single-agent trials, if applicable.

3.1.6. Life expectancy of greater than 3 months in the opinion of the investigator.

3.1.7. ECOG performance status 0 or 1 (Karnofsky >70%; see Appendix A).

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

- leukocytes	$\geq$3,000/mcL
- absolute neutrophil count	$\geq$1,500/mcL
- platelets	$\geq$100,000/mcL
- total bilirubin	within 1.5 x institutional upper limit of normal
- AST(SGOT)/ALT(SGPT)	$\leq$2.5 X institutional upper limit of normal
- creatinine	within 1.5 x institutional upper limit of normal
OR	
- creatinine clearance	$\geq$60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

3.1.9. Urine protein should be screened by urinalysis for Urine Protein Creatinine Ratio (UPCR). For UPCR > 1, a 24-hour urine protein should be obtained and the level should be <500 mg.

3.1.10. Patients on full-dose anticoagulants (e.g., warfarin) with PT INR >1.5 are eligible

provided that both of the following criteria are met:

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

b) The patient has no active bleeding or pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices).

3.1.11. Pulmonary: FEV1 > 2.0 liters or > 75% of predicted for height and age. (PFTs are required for patients over 50 years old or with significant pulmonary or smoking history).

3.1.12. Cardiac: No evidence of congestive heart failure, symptoms of coronary artery disease, myocardial infarction less than 6 months prior to entry, serious cardiac arrhythmias, or unstable angina.

Patients who are over 40 years old or have had previous myocardial infarction greater than 6 months prior to study entry or have significant cardiac family history (CAD or serious arrhythmias) will be required to have a negative or low probability cardiac stress test (for example, thallium stress test, stress MUGA, stress echo or exercise stress test) for cardiac ischemia within 8 weeks prior to registration.
An echocardiogram should be performed at baseline in all patients. Ejection fraction (EF) from baseline echocardiogram must be within the institutional limits of normal as determined by the reading cardiologist. If the baseline cardiac stress test incorporates an echocardiogram, then this will not need to be done again at baseline.

3.1.13. CNS: No history of cerebrovascular accident or transient ischemic attacks within the past 6 months.

3.1.14. Although clinical data are lacking on the immediate or long-term effects of aflibercept on the developing human fetus, the agent is teratogenic and negatively affects fetal development in animal models. For this reason and because antiangiogenic agents as well as other therapeutic agents used in this trial are known to be teratogenic, 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 at least 6 months after completion of study therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

Women should not be lactating and, if of childbearing age, should have a negative pregnancy test (b-HCG test; serum or urine, minimum sensitivity 25 IU/L or equivalent units of b-HCG) within two week of registration in the study.

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

3.2. Exclusion Criteria

3.2.1. Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.2. Patients may not be receiving any other investigational agents.

3.2.3. Patients with brain metastases should be excluded from this clinical trial except as noted above under section 3.1.3.

3.2.4. Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies, and patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to other agents used in the study.

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

3.2.6. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days of treatment.

3.2.7. Patients with the following invasive procedures:
- major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to Day 1 therapy.
- anticipation of need for major surgical procedures during the course of the study.
- minor surgical procedures, fine needle aspirations or core biopsies within 7 days prior to Day 1 of therapy. Central venous catheter placements are permitted to be completed 7 or more days prior to Day 1 of therapy. However, peripherally inserted central catheter (PICC or PIC line) may be placed at any time prior to or during therapy.

3.2.8. Patients with clinically significant cardiovascular or cerebrovascular disease:
- history of cerebrovascular accident or transient ischemic attack within past 6 months
- uncontrolled hypertension, defined as blood pressure >150/100 mm Hg or systolic BP >180 mm Hg if diastolic blood pressure <90 mm Hg, on at least 2 repeated determinations on separate days within past 3 months.
- myocardial infarction, CABG or unstable angina within the past 6 Months.
- New York Heart Association grade III or greater congestive heart failure (Appendix E), serious cardiac arrhythmia requiring medication, unstable angina pectoris within past 6 months.
- clinically significant peripheral vascular disease within past 6 months.

• Pulmonary embolism, DVT, or other thromboembolic event within past 6 months.

3.2.9. History of tumor-related or other serious hemorrhage, bleeding diathesis, or underlying coagulopathy.

3.2.10. PT INR >1.5 unless the patient is on full-dose warfarin.

3.2.11. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.12. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with VEGF Trap. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.2.13. Patients who have other current malignancies are not eligible. Patients with other malignancies are eligible if they have been continuously disease free for > 5 years prior to the time of randomization. Patients with prior history at any time of any in situ cancer, lobular carcinoma of the breast in situ, cervical cancer in situ, atypical melanocytic hyperplasia or melanoma in situ are eligible. Patients with prior history of basal or squamous skin cancer are eligible. Patients who have had multiple primary melanomas are eligible.

3.2.14. Patients must not have autoimmune disorders or conditions of immunosuppression that require current ongoing treatment with systemic corticosteroids (or other systemic immunosuppressants), including oral steroids (i.e., prednisone, dexamethasone) or continuous use of topical steroid creams or ointments or ophthalmologic steroids or steroid inhalers.

If a patient had been taking steroids, at least 2 weeks must have passed since the last dose.

3.3. Inclusion of Women and Minorities

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

Accrual Targets

Ethnic Category	Sex/Gender					
	Females		Males		Total	
Hispanic or Latino	6	+	5	=	11	
Not Hispanic or Latino	39	+	55	=	94	
Ethnic Category: Total of all subjects	45 (A1)	+	60 (B1)	=	105	(C1)
Racial Category						

American Indian or Alaskan Native	0		+	0		=	0
Asian	2		+	1		=	3
Black or African American	0		+	0		=	0
Native Hawaiian or other Pacific Islander	0		+	0		=	0
White	43		+	59		=	102
Racial Category: Total of all subjects	45	(A2)	+	60	(B2)	=	105 (C2)

These numbers are based on the actual historical accrual demographics at City of Hope National Medical Center only for patients with melanoma, but these estimates will vary with the other CCCP sites (or other consortia sites) accruing from the different catchment areas. In addition, the study investigators strongly believe in improving the accrual rates of non-white patients and therefore would like to express their strong commitment to make an improvement over these historical accrual numbers at COH as listed in the accrual targets table.

4. REGISTRATION PROCEDURES

4.1. General Guidelines

Eligible patients will be entered on study centrally at the California Cancer Consortium Data Coordinating Center (DCC) at the City of Hope. All sites should call the DCC at (626) 256-4673 extension 65928 to verify slot availabilities.

Following registration, patients should begin protocol treatment within 1 week. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The DCC should be notified of cancellations as soon as possible.

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

4.2. Registration Process

Once the signed informed consent has been obtained, all pretreatment evaluations have been performed, and patient's eligibility has been confirmed by the data coordinating center a patient will be entered on study.

To register a patient, the research nurse or data manager must complete the eligibility/registration form and contact the Consortium office (Data Coordinating Center for the California Cancer Consortium) at the City of Hope (626-256-4673, ext. 65928), FAX a copy of the completed eligibility checklist, required pre-study tests (laboratory and pathology report), signed Informed Consent, signed Patients' Bill of Rights and HIPAA authorization form. (FAX Number: 626-256-8654). See Appendix

C ("Registration Procedures")

The research nurse or data manager at the participating site will then call the Data Coordinating Center at Tel# 626-256-4673 extension 65928 to confirm receipt of all registration documents. To complete the registration process, the data coordinating center coordinator will:

- Verify the eligibility
- Register the patient on study
- Assign a patient accession number
- Fax or e-mail the patient study number and dose to the participating site
- Call the research nurse or data manager at the participating site and verbally confirm registration.

5. TREATMENT PLAN

5.1. Overall Treatment Plan

Definitions:

1. A **cycle of IL-2**: eligible patients receive high-dose IL-2 at 600,000 IU/kg IV every 8 hours for up to 14 doses. This constitutes one cycle of IL-2.
2. A **cycle of Aflibercept**: eligible patients receive aflibercept at 3 mg/kg (combination phase) or 4 mg/kg (maintenance phase) IV every 2 weeks. This constitutes one cycle of aflibercept.
3. The **combination phase (Arm A)**: during this phase, IL-2 and aflibercept will be given concurrently. It consists of 3 courses of combination therapy.
   a. Each course consists of 2 cycles of IL-2 as follows: high-dose IL-2 at 600,000 IU/kg is given IV every 8 hours for up to 14 doses (one cycle), followed by a rest period of 1-2 weeks and readmission for a second high dose IL-2 cycle for up to 14 doses (2^{nd} cycle).
   b. In addition, aflibercept will be given concurrently at 3 mg/kg IV every 2 weeks, but in course 1 only aflibercept will start 2 weeks prior to IL-2. Therefore, course 1 will consist of 5 cycles of aflibercept, while courses 2 and 3 will consist of 4 cycles of aflibercept each.
   c. Based on the occurrence of treatment-related toxicities and requirements for dose adjustments or delays, a patient may or may not receive the full planned treatment, but response assessment will continue to be carried out at the end of each course.
4. The **maintenance phase (Arm A)**: only aflibercept monotherapy will be given during this phase at 4 mg/kg IV every 2 weeks. Response assessment will be carried out every 12 weeks (6 cycles of aflibercept) for the first 2 years, then every 6 months (-/+ 2 weeks) for years 3-5, then yearly (-/+ 4 weeks) afterwards.

The planned treatment for Arm A consists of 3 courses of combination aflibercept and high dose IL-2 (the combination phase) followed by maintenance aflibercept

monotherapy (aflibercept monotherapy phase). Arm B is high dose IL-2 alone. Response assessment will occur at the end of each course of combination therapy (arm A) and patients without evidence of disease progression (RECIST v.1.1) or limiting toxicities will be offered additional courses of treatment (or maintenance aflibercept therapy).

Management and dose modifications associated with the above adverse events are outlined in Section 6.

Arm A:Course 1 (consists of 10 weeks): Aflibercept to be given at **3 mg/kg** IV on day 1 of weeks 1, 3, 5, 7 and 9. HD IL-2 will be given at 600,000 U/kg/dose IV Q8h x 5 days (max 14 doses) starting on day 1 of weeks 3 and 5. Response assessment will be done during week 10.

Arm A: Courses 2 and 3 (consist of 8 weeks each): Patients with evidence of SD, PR or CR on response assessment will be offered additional courses of therapy up to a total of 3 courses. During courses 2 and 3, aflibercept will be given at **3 mg/kg** on day 1 of weeks 1, 3, 5 and 7. HD IL-2 will be given at 600,000 U/kg/dose IV Q8h x 5 days (max 14 doses) starting on day 1 of weeks 1 and 3.

Arm A: Maintenance aflibercept monotherapy: Following response assessment after course 3 of combination therapy and after resolution of all toxicities to ≤ grade 1 (CTCAE v.4), aflibercept monotherapy will be initiated to be administered at **4 mg/kg** IV on Day 1of each 14-day cycle. Plus or minus 2-day time windows for each treatment day are permitted, as are treatment delays of up to 2 weeks in case of unresolved toxicity. In this case, **blood pressure monitoring should be done weekly for the first 3 weeks of the maintenance phase to ensure tolerance of the higher aflibercept dose.** However, if the aflibercept dose had to be reduced during the combination phase due to aflibercept-related toxicities, then that reduced dose will be used for maintenance therapy. No need for weekly monitoring of blood pressure, if the reduced dose has already been demonstrated to be tolerable.

	Course 1 (Arm A)									
Course 1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10
Aflibercept 3 mg/kg IV	X		X		X		X		X	
HD IL-2 600,000 U/kg/dose IV Q8h x 5 days			X		X					

(max 14 doses)										
Response Assessment										X

	Course 2 (Arm A)								Course 3 (Arm A)							
Courses 2-3	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8
Aflibercept 3 mg/kg IV	X		X		X		X		X		X		X		X	
HD IL-2 600,000 U/kg/dose IV Q8h x 5 days (max 14 doses)	X		X						X		X					
Response Assessment								X								X

Blood samples for the purpose of measuring serum VEGF levels or other laboratory corollary studies will be collected at the multiple time points as noted in section 9.1.1. See Section 9.1.1 for handling, processing, and shipping procedures**.**

For arm B, patients will receive HD IL-2 alone following the institutional standard of care guidelines. Patients will receive a maximum of 3 courses (6 cycles; 1 course of IL_2 in arm B = 2 cycles of IL-2). Response assessment will be carried out at the end of each course. In the absence of disease progression by RECIST v.1.1, patients will be offered additional courses of therapy for a maximum of 3 courses (6 cycles).

5.2. Aflibercept Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications for aflibercept are described in Section 6.

- Patients will receive a dose of aflibercept administered IV on Day 1 of each 14-day cycle. Plus or minus 2-day time windows for each treatment day are permitted, as are treatment delays of up to 2 weeks in case of unresolved toxicity. Aflibercept will be administered as an IV infusion over at least 1 hour

into a peripheral vein or a central venous catheter via a system that is compatible with aflibercept.

- The dosing solutions will be prepared by diluting aflibercept concentrate (25 mg/mL) with the appropriate volume of 0.9% NaCl or 5% dextrose to a final concentration between 0.6 mg/mL and 8 mg/mL. This will be administered intravenously over at least 1 hour into a peripheral vein or central venous catheter using an infusion pump. CADD Legacy pump will be used for the infusion. See Section 8.1.1 on other suitable delivery devices that are allowed.
- Doses may be modified for toxicity as described in Section 6. New cycles of therapy may not begin until any aflibercept -related adverse events have adequately resolved. The Principal Investigator should be contacted for any treatment delay of >2 weeks duration.

Special Cautions/Safety Issues

- **Infusion and hypersensitivity reactions** (*e.g.*, rash, urticaria, fever, rigors, hypertension, wheezing, or hypoxia) may occur during or shortly after IV administration of protein therapeutics. The most appropriate premedication regimen for use with aflibercept has not been determined, and patients should not be given prophylactic premedication for acute infusion reactions without prior discussion with the NCI Senior Investigator.

  If infusion hypersensitivity reactions occur in a given patient, then institutional treatment guidelines for similar therapeutic agents should be followed. Subsequent doses of aflibercept should not be given without prior consultation with the NCI Senior Investigator to discuss appropriate premedication, and should be accompanied by an increased level of vigilance in observation and monitoring, administration of premedications, etc. However, dose reductions will not be made for acute infusion reactions.

  If a patient experiences a hypersensitivity or infusion reaction to aflibercept, serum should be obtained to evaluate for anti-aflibercept antibody formation at the time of the reaction. Please see section 9.2 for serum sample collection, preparation and shipping.

- Since aflibercept is a protein, it is possible that patients might experience **allergic or immunologic reactions** to aflibercept administration. If a potentially immune-mediated event occurs during infusion of study drug, the ongoing infusion will be stopped immediately. Following any potentially immunologic toxicity, dosing may not be resumed until the event has been reviewed by the investigator and the NCI Senior Investigator, and a plan of management has been formulated.

- **Hypertension** is a known and potentially serious adverse event associated with aflibercept treatment. Patients should have their blood pressure monitored weekly during the first cycle of therapy and prior to each infusion of aflibercept.

Aflibercept treatment modifications due to hypertension should follow the instructions in Section 6.1.

- Given the potential for **hemorrhage or wound healing complications** with aflibercept, the agent should not be administered ≤ 48 hours following minor surgical procedures (e.g., fine needle biopsy/aspiration, placement of a central venous access device, or removal/biopsy of a skin lesion), or until evidence of wound healing (e.g., scab formation) is observed, whichever is longer.

- Given the potential for osteonecrosis of the jaw with aflibercept in patients who have had previous radiation to the head and neck, special attention should be given to any complaints of jaw pain, oral pain or sore mouth.

- Any patient with an anti- aflibercept (VEGF Trap) antibody level above the limit of quantitation who develops a grade ≥2 systemic immunologic adverse effect considered at least possibly related to study drug, will be permanently discontinued from study drug administration.

- Any patient with an anti- aflibercept (VEGF Trap) antibody level above the limit of quantitation who develops one of the following will be permanently discontinued from study treatment:
  − 24-hour urine protein total >3.5 grams, or
  − confirmed doubling of the baseline serum creatinine to a level >1.5 x ULN while in a well-hydrated state, or
  − confirmed doubling of the baseline BUN to a level >1.5 x ULN while in a well-hydrated state

5.3. Aldesleukin (Interleukin-2) Administration

Aldesleukin (Interleukin-2, IL-2) will be administered on an inpatient basis. Reported adverse events and potential risks for aldesleukin are described in Section 7.

- Patients will receive a total of 6 cycles (1 cycle = 5 days) of IL-2 as described in section 5.1. A cycle of IL-2 may be delayed for up to 2 weeks in case of unresolved toxicity.

- Aldesleukin will be administered at 600,000 IU/kg IV bolus q 8 hours during days 1-5 of each cycle (maximum 14 doses per 5 day cycle).

- For arm A (combination arm), dose 1 of aldesleukin on day 1 of each cycle of IL-2 will be administered after aflibercept given on that day.

- For arm A (combination arm) an echocardiogram will be performed at baseline and following each course of therapy (week 10 of course 1 and week 8 of courses 2 and 3). Evidence of cardiac dysfunction compared to baseline

(decrease in ejection fraction by 25% or more) will lead to treatment discontinuation. For arm B, there is no requirement to repeat the echocardiogram following each course of IL-2 therapy unless it is clinically indicated.

NOTE: Ejection fraction (EF) from baseline echocardiogram done on arm A must be within the institutional limits of normal as determined by the reading cardiologist. For patients who are required to have a baseline cardiac stress test, if the baseline cardiac stress test incorporates an echocardiogram, then this will not need to be done again at baseline. For subsequent echocardiograms, evidence of cardiac dysfunction compared to baseline (decrease in ejection fraction by 25% or more) will lead to treatment discontinuation.

- As all institutions participating in this protocol have established and experienced high dose interleukin-2 programs, the administration of aldesleukin (at the protocol's specified dose and frequency) and the dose delay/discontinuation criteria during a cycle of IL-2 will follow the institutional standard of care guidelines. A useful guide is provided by Schwartzentruber DJ. J Immunother. 2001 Jul-Aug;24(4):287-93[21].

- For patients receiving high dose IL-2 on Arm A or B and who take anti-hypertensive medications, it is recommended that the blood pressure medications be managed as follows (**individual variations are acceptable at the discretion of the treating physician when it is felt in the best interest of the patient**):
    - On the day of admission, the morning blood pressure medications should be taken, if the first dose of IL-2 is expected to be given that evening and not during the day. Otherwise, if the first dose of IL-2 is expected to be given during the day, then the morning blood pressure medications should be held. The goal is two-fold:
        - Avoid uncontrolled hypertension in patients holding the AM antihypertensive medications, if the dose will be delayed till the evening.
        - Avoid excessive hypotension during IL-2 if the AM dose was given and the first dose of IL-2 was given during the day.
    - If the first dose of IL-2 is anticipated to be given in the evening of the day of admission, then the blood pressure medications should be held for that evening and throughout IL-2 treatment unless otherwise specified by the treating physician.
    - Upon completion of IL-2 therapy, the blood pressure medications should restarted as soon as the IL-2 induced hypotension (low blood pressure) has resolved. Most importantly, the blood pressure medications should be restarted before the patient is discharged home, unless the patient was found to be hypotensive and the treating physician decides to closely monitor the blood pressure before initiating the

antihypertensive medications.

5.4. General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of aflibercpt with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. All patient treatments 30 days prior to registration onto the study, at any time during the study, and up to 60 days after the end of the study will be considered as concomitant treatments. Any treatment administered following the withdrawal from the study that is used to treat new or unresolved events related to the study treatment, is also considered as concomitant treatment. The type, dose, and route of administration for all concomitant treatments must be documented in the case report form (CRF).

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the investigational products, they may be given at the discretion of the investigator and recorded in the CRF.

The following concomitant treatments are permitted during this study:

- all supportive measures (including hyperalimentation and blood transfusions) consistent with optimal patient care.
- medications for chronic pain management, including narcotic analgesics, are permitted as clinically indicated.
- therapeutic use of hematopoietic growth factors is permitted at the investigator's discretion and should follow American Society of Clinical Oncology guidelines for their use.

5.5. Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for per study protocol until one of the following criteria applies:

X Disease progression,

X Intercurrent illness that prevents further administration of treatment,

X Unacceptable adverse events(s),

X Patient decides to withdraw from the study, or

X General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator,

X Arterial thromboembolic events including cerebrovascular accidents, myocardial infarctions, transient ischemic attacks, new onset or worsening of pre-exiting angina,

X Evidence of cardiac dysfunction (decrease in ejection fraction by 25% or more) compared to baseline noted on study echocardiogram testing,

5.6. Duration of Follow Up

Patients will be followed for 5 years after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. The frequency and the type of evaluations during this follow up period will follow institutional standard of care practices. For patients who wish not to follow with a study investigator, they can be followed by their treating physician of choice and also following local standard of care practices. Data on disease progression and survival will be collected on all patients every 3-4 months.

6. DOSING DELAYS/DOSE MODIFICATIONS (Aflibercept)

NOTE: As all institutions participating in this protocol have established and experienced high dose interleukin-2 programs, the administration of aldesleukin (at the protocol's specified dose and frequency) and the dose delay/discontinuation criteria during a cycle of IL-2 will follow the institutional standard of care guidelines. A useful guide is provided by Schwartzentruber DJ. J Immunother. 2001 Jul-Aug;24(4):287-93[21].

Aflibercept doses will be modified as shown below. Doses reduced for drug-related toxicity should generally not be re-escalated, even if the reduced dose produces minimal or no toxicity.

Dose Levels for Dose Reduction

Dose Level	Aflibercept	
0	4 mg/kg	3 mg/kg
-1	3 mg/kg	2 mg/kg
-2	2 mg/kg	1 mg/kg

The lowest dose level will be utilized for patients requiring multiple simultaneous dose adjustments. **No more than 2 aflibercept dose reductions per patient are permitted.** Patients requiring more than 2 aflibercept dose reductions will have aflibercept permanently discontinued. Unless otherwise indicated, all grades of toxicity refer to NCI CTCAE v.4.0 grades.

- Frequent blood pressure monitoring is important in patients receiving aflibercept. Patients should seek **immediate** medical advice if their blood pressure (BP) exceeds 180 mmHg (systolic) or 105 mmHg (diastolic) at any time and should also be encouraged to contact their physician if they are concerned about any symptoms that may be associated with high blood pressure (*e.g.*, headache).

- Renal function (creatinine and urinary protein) should be frequently monitored as suggested by the pathologic changes noted in animal studies and evidence from studies of other antiangiogenic agents. Specific guidelines for management of proteinuria are presented in Section 6.2.

In the absence of disease progression or limiting toxicities, patients may continue IL-2 therapy per study protocol even if aflibercept was permanently discontinued.

6.1. Management of Hypertension

Increases in blood pressure (BP) and cases of hypertension have been associated with many drugs acting on the VEGF pathway. The proposed mechanism for this increase is through inhibition of VEGF-induced peripheral vasodilation. Hypertension following aflibercept treatment has been seen in animal studies as well as clinical trials.

Notes:

- **<u>While patients are receiving treatment with aflibercept</u>, the early initiation of antihypertensive treatment for grade 1 or 2 hypertension to minimize more severe or persistent hypertension is not considered a grade 3 adverse event.**

- Decisions to hold or decrease the aflibercept dose during treatment must be based on BP readings taken in the clinic by a medical professional.

- In case of new-onset or worsening (grade ≥ 2) hypertension, see chart on page 24. Other preferred treatment options include calcium-channel blockers or alpha-1 blockers. Angiotensin converting enzyme inhibitors or angiotensin II antagonists may also be appropriate in the absence of significant renal dysfunction or suspicion of renovascular disease. Beta blockers and diuretics should be used with caution due to their relatively slow onset of action. Ultimately, antihypertensive treatment must be individualized based on the presence of comorbidity such as diabetes, cardiovascular, or renal disease, additionally taking into account the safety and efficacy of any prior antihypertensive therapy received. In addition, oral and/or intravenous sodium intake should be carefully monitored in these patients. Blood pressure and electrolyte monitoring should be performed at least once or twice weekly until stable blood pressure control is achieved. Early consultation with a cardiologist is strongly encouraged in case of uncontrolled hypertension.

- The following table is a recommendation:

Hypertension Monitoring and Management			
Grade (CTCAEv4.0)	**Antihypertensive Therapy**	**Blood Pressure Monitoring**	**Aflibercept Dose Modification**
Grade 1	• None (Consider initiating therapy of choice per MD &/**OR** Increase doses of existing medications) • Baseline	• Standard monitoring per study protocol • In addition, start daily BP monitoring at home and plan to start treatment for grade 2 HTN	No Change
Grade 2- Mild	• Initiate therapy of choice per MD &/**OR** • Increase doses of existing medications until BP controlled or at maximum dose	• Increased frequency of monitoring until stabilized	No Change
Persistent Moderate Hypertension **(Definition:** Patients who initiate antihypertensive therapy or have additional medications added to existing therapy but their BP is not controlled to grade 1 or less)	• Initiate therapy of choice per MD &/**OR** • Increase doses or number of medications until BP controlled or at maximum dose	• Increased frequency of monitoring until stabilized *e.g*. every 48 hours • Supervised by healthcare professional	If partial or no control and BP still in a moderate range for 24-48 hours, **hold aflibercept and add additional drugs**, increasing to a maximum dose until hypertension controlled; Monitor for hypotension; **Decrease aflibercept by 1 dose level**
Grade 3- Severe	• Start immediate therapy with 2 drug combination including at least a DHP- CCB • Escalate doses to achieve optimal control of BP, up to the maximum dose • If partial or no BP control, add additional drugs up to 4; increase to optimal or maximum doses of all drugs	• Increased frequency of monitoring until stabilized *e.g*. every 48 hours • Supervised by healthcare professional	**Hold aflibercept**; If control of BP in the Mild range, restart VEGF TRAP at the next lower dose level If partial or no control, **discontinue therapy per investigator** **Stop aflibercept** if hypertension is symptomatic, hospitalize patient

			for management of BP
Grade 4 Hypertensive Crisis	• Optimal management with intensive support IV in ICU	• Hospitalize patient for management	Off protocol therapy; **Discontinue aflibercept;** **Monitor closely for hypotension**
• Abbreviations: dihydropyridine calcium-channel blockers (DHP-CCB), selective beta blockers (BB), Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin II Receptor Blockers (ARB) • If patients require a delay of > 2 weeks for management of hypertension, discontinue aflibercept therapy • If patients require > 2 dose reductions, discontinue aflibercept therapy • Patients may have up to 2 drugs for management of hypertension prior to any dose reduction in aflibercept • 24-48 hour should elapse between modifications of antihypertensive therapy • Hypertension should be graded using the NCI CTCAEv4.0			

6.2. Proteinuria

A 24-hour urine collection for quantitative protein determination must be obtained for a urine protein:creatinine ratio (UPCR) >1. Instructions for dose modifications due to proteinuria are summarized below.

Proteinuria	Action to be Taken
Grade ≤ 2	No modification.
Grade 3 (4+ or >3.5 grams/24 hours)	• Delay dosing until recovery to urinary protein <2 grams/24 hours. • Reduce subsequent doses of aflibercept by 1 dose level if proteinuria does not recover to <2 grams/24 hours within 2 weeks. • Discontinue patients from aflibercept treatment who experience recurrent Grade 3 toxicity after 2 dose reductions.
Grade 4	Consult a nephrologist and discontinue patient from aflibercept treatment.

6.3. Other Adverse Events

- No dose modifications should be performed for adverse events (such as alopecia) that do not directly affect the patient's physical health.

- Dose-reduce aflibercept for grade 3 or 4 aflibercept-related adverse events aside from hypertension and proteinuria even if therapy is not delayed. **Exception:** Patients with grade 3 or 4 electrolyte or other laboratory abnormalities that could be corrected within 48 hours to grade 2 or less could be retreated with the same dose of aflibercept. Re-treatment with aflibercept could be done as soon as these abnormalities have been corrected to grade 2 or less.

- Any other drug-related adverse event considered serious or which causes a >2-week

study treatment delay will result in the reduction of subsequent doses by one dose level. If patient cannot restart therapy after 2 weeks delay, contact the Principal Investigator for discussion of removing patient from study.

- Other aflibercept dose reductions not described above may be performed at the discretion of the investigator after discussion with the NCI Senior Investigator, provided that criteria for patient withdrawal from study treatment (described in Section 5.5) have not been met.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

7.1. Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

7.1.1. CAEPR for Aflibercept (VEGF-Trap, NSC 724770)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm for further clarification. *Frequency is provided based on 811 patients.* Below is the CAEPR for aflibercept (VEGF-Trap).

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

Adverse Events with Possible Relationship to Ziv-aflibercept (VEGF-Trap, AVE 0005) (CTCAE 4.0 Term) [n= 811]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
		Febrile neutropenia	
		Hemolytic uremic syndrome	
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Chest pain - cardiac	
		Myocardial infarction	
		Restrictive cardiomyopathy	
		Cardiac disorders - Other (intracardiac thrombus)	
GASTROINTESTINAL DISORDERS			
Abdominal pain			***Abdominal pain (Gr 2)***
	Anal mucositis		
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
		Gastrointestinal fistula[2]	
		Gastrointestinal perforation[3]	
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Pain		
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			

Adverse Events with Possible Relationship to Ziv-aflibercept (VEGF-Trap, AVE 0005) (CTCAE 4.0 Term) [n= 811]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Wound complication		
	Wound dehiscence		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		
Lymphocyte count decreased			***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		
	Myalgia		***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Headache			***Headache (Gr 3)***
		Ischemia cerebrovascular	***Ischemia cerebrovascular (Gr 2)***
		Reversible posterior leukoencephalopathy syndrome	
		Transient ischemic attack	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	

Adverse Events with Possible Relationship to Ziv-aflibercept (VEGF-Trap, AVE 0005) (CTCAE 4.0 Term) [n= 811]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Proteinuria		***Proteinuria (Gr 3)***
		Renal disorders - Other (nephrotic syndrome)	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
	Genitourinary system fistula[5]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Pharyngolaryngeal pain		
Voice alteration			***Voice alteration (Gr 2)***
	Respiratory, thoracic, and mediastinal disorders - Other (rhinorrhea)		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Palmar-plantar erythrodysesthesia syndrome		
	Rash maculo-papular		
	Skin hyperpigmentation		
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 3)***
	Vascular disorders - Other (hemorrhage)[6]		***Vascular disorders - Other (hemorrhage)[6] (Gr 2)***

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

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

[3]Gastrointestinal perforation imay include: Colonic perforation, Duodenal perforation,

Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (hemoglobin increased); Hemolysis
CARDIAC DISORDERS - Acute coronary syndrome; Cardiac disorders - Other (left ventricular diastolic dysfunction); Heart failure; Left ventricular systolic dysfunction; Pericarditis; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus; Vertigo
ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Extraocular muscle paresis; Eye disorders - Other (blindness transient); Eye disorders - Other (diplopia); Vitreous hemorrhage
GASTROINTESTINAL DISORDERS - Abdominal distension; Colitis; Dental caries; Dry mouth; Dyspepsia; Dysphagia; Esophageal pain; Flatulence; Gastritis; Gastrointestinal disorders - Other (early satiety); Gastrointestinal disorders - Other (enteric fistula); Gastrointestinal disorders - Other (eructation); Gastrointestinal disorders - Other (gastrointestinal necrosis); Gastrointestinal disorders - Other (hiatal hernia);Gastrointestinal disorders - Other (intestinal ischemia); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal disorders - Other (peritonitis); Gingival pain; Hemorrhoids; Ileus; Oral pain; Rectal mucositis; Rectal ulcer; Small intestinal mucositis; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema trunk; Facial pain; Infusion related reaction; Injection site reaction; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Cholecystitis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Biliary anastomotic leak; Gastric anastomotic leak; Vascular access complication
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; Creatinine increased; Ejection fraction decreased; GGT increased; Investigations - Other (elevated LDH)
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperglycemia;

Hyperkalemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Avascular necrosis; Chest wall pain; Generalized muscle weakness; Head soft tissue necrosis; Joint range of motion decreased; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Musculoskeletal and connective tissue disorder - Other (musculoskeletal stiffness); Musculoskeletal and connective tissue disorder - Other (rotator cuff tear); Myositis; Neck pain; Osteonecrosis of jaw; Pain in extremity; Pelvic soft tissue necrosis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage)
NERVOUS SYSTEM DISORDERS - Amnesia; Ataxia; Cognitive disturbance; Dysgeusia; Encephalopathy; Extrapyramidal disorder; Leukoencephalopathy; Memory impairment; Paresthesia; Peripheral sensory neuropathy; Seizure; Syncope; Vagus nerve disorder
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia; Psychiatric disorders - Other (mental status change); Psychosis
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Hypoxia; Laryngeal mucositis; Nasal congestion; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary fibrosis; Respiratory, thoracic and mediastinal disorders - Other (nasal dryness); Respiratory, thoracic and mediastinal disorders - Other (tracheal fistula); Respiratory, thoracic and mediastinal disorders - Other (septal perforation); Tracheal mucositis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Nail loss; Rash acneiform; Skin and subcutaneous tissue disorders - Other (hyperemia); Skin ulceration
VASCULAR DISORDERS - Hematoma; Hypotension; Peripheral ischemia; Phlebitis

Note: Ziv-aflibercept (VEGF-Trap, AVE 0005) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.2. CAEPR for Interleukin-2 (NSC 373364)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with bold and italicized text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for interleukin-2.

Adverse Events with Possible Relationship to Interleukin-2 (CTCAE 4.0 Term)		EXPECTED AEs FOR CTEP-AERS REPORTING Agent Specific Adverse Event List (ASAEL)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		***Expected***
	Anemia	***Anemia***
CARDIAC DISORDERS		
	Conduction disorder	***Conduction disorder***
	Left ventricular systolic dysfunction	***Left ventricular systolic dysfunction***
	Myocardial infarction	
	Myocarditis	***Myocarditis***
	Palpitations	***Palpitations***
	Sinus tachycardia	***Sinus tachycardia***
	Supraventricular tachycardia	***Supraventricular tachycardia***
	Ventricular arrhythmia	***Ventricular arrhythmia***
EAR AND LABYRINTH DISORDERS		
	Hearing impaired	***Hearing impaired***
EYE DISORDERS		
	Blurred vision	***Blurred vision***
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Diarrhea	***Diarrhea***
	Dry mouth	***Dry mouth***
	Gastrointestinal disorders - Other (Perforation, GI – Select)	
	Gastrointestinal disorders - Other (small bowel fistula)	***Gastrointestinal disorders - Other (small bowel fistula)***
	Mucositis oral	***Mucositis oral***
	Nausea	***Nausea***
	Vomiting	***Vomiting***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	***Chills***
	Edema limbs	***Edema limbs***

	Fatigue	***Fatigue***
	Fever	***Fever***
IMMUNE SYSTEM DISORDERS		
	Allergic reaction	***Allergic reaction***
	Autoimmune disorder	***Autoimmune disorder***
INFECTIONS AND INFESTATIONS		
	Infections and Infestations – Other (Infection – Select)	***Infections and Infestations – Other (Infection – Select)***
INVESTIGATIONS		
	Activated partial thromboplastin time prolonged	***Activated partial thromboplastin time prolonged***
	Alanine aminotransferase increased	***Alanine aminotransferase increased***
	Alkaline phosphatase increased	***Alkaline phosphatase increased***
	Aspartate aminotransferase increased	***Aspartate aminotransferase increased***
	Blood bilirubin increased	***Blood bilirubin increased***
	Creatinine increased	***Creatinine increased***
	GGT increased	***GGT increased***
	INR increased	***INR increased***
	Platelet count decreased	***Platelet count decreased***
	Weight gain	***Weight gain***
	White blood cell decreased	***White blood cell decreased***
METABOLISM AND NUTRITION DISORDERS		
	Acidosis	***Acidosis***
	Anorexia	
	Hyperuricemia	***Hyperuricemia***
	Hypocalcemia	***Hypocalcemia***
	Hypoglycemia	***Hypoglycemia***
	Hypomagnesemia	
	Hyponatremia	***Hyponatremia***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	***Arthralgia***
	Myalgia	***Myalgia***
	Myositis	***Myositis***
NERVOUS SYSTEM DISORDERS		
	Depressed level of consciousness	***Depressed level of consciousness***
	Dizziness	
	Headache	***Headache***
	Memory impairment	***Memory impairment***
	Nervous system disorders - Other (sleep	***Nervous system disorders - Other***

	disturbances)	***(sleep disturbances)***
	Peripheral sensory neuropathy	***Peripheral sensory neuropathy***
	Seizure	***Seizure***
PSYCHIATRIC DISORDERS		
	Anxiety	
	Confusion	***Confusion***
	Personality change	***Personality change***
	Psychosis	***Psychosis***
RENAL AND URINARY DISORDERS		
	Acute kidney injury	***Acute kidney injury***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Adult respiratory distress syndrome	***Adult respiratory distress syndrome***
	Allergic rhinitis	***Allergic rhinitis***
	Apnea	
	Cough	
	Dyspnea	***Dyspnea***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	***Alopecia***
	Pruritus	***Pruritus***
	Rash maculo-papular	***Rash maculo-papular***
VASCULAR DISORDERS		
	Capillary leak syndrome	***Capillary leak syndrome***
	Hypotension	***Hypotension***
	Peripheral ischemia	
	Thromboembolic event	
	Vascular disorders - Other (vasodilation)	

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

Also reported on interleukin-2 trials but with the relationship to interleukin-2 still undetermined:

CARDIAC DISORDERS - Mobitz type I; Pericardial effusion
EYE DISORDERS - Eye disorders - Other (mydriasis)
GASTROINTESTINAL DISORDERS - Gastrointestinal disorders – Other (Hemorrhage, GI – Select); Pancreatitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - General disorders and administration site conditions - Other (phospholipid syndrome); Hypothermia; Multi-organ failure

INFECTIONS AND INFESTATIONS – Infections and infestations – Other (Infection (documented clinically or microbiologically with Grade 3 or 4 neutrophils [ANC <1.0 x 10e9/L]) – Select)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Soft tissue necrosis lower limb
NERVOUS SYSTEM DISORDERS - Encephalopathy; Syncope
PSYCHIATRIC DISORDERS - Agitation
RENAL AND URINARY DISORDERS - Renal and urinary disorders - Other (acute tubular necrosis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Bronchospasm; Hypoxia; Pneumothorax; Pulmonary edema
VASCULAR DISORDERS – Phlebitis, splenic infarction (in a patient with a history of thrombocytosis treated with the combination of IL2 and aflibercept).

Note: Interleukin-2 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.2.1. Protocol-Specific Expedited Adverse Event Reporting Exclusions for Interleukin-2 related Adverse Events

- For this protocol only, certain interleukin-2 related AEs/grades are exceptions to the Expedited Reporting Guidelines and do not require expedited reporting (*i.e.*, CTEP-AERS). The following interleukin-2 related AEs must be reported only if they exceed the grade listed below through the routine reporting mechanism (Section 7.4):

  Lymphocyte count decreased (Gr 4)
  Neutrophil count decreased (Gr 4)
  Platelet count decreased (Gr 4)
  White blood cell decreased (Gr 2)
  Dyspnea (Gr 3)
  Fatigue (Gr 3)
  Headache (Gr 3)
  Nausea (Gr 3)
  Vomiting (Gr 2)
  Diarrhea (Gr 2)
  Anemia (Gr 2)
  Abdominal pain (Gr 2)
  Fever (Gr 2)
  Edema limbs (Gr 2)
  Anorexia (Gr 2)
  Arthralgia (Gr 2)
  Myalgia (Gr 2)
  Cough (Gr 2)

Hypophosphatemia, Gr 3

7.2. Adverse Event Characteristics

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

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are ***bold and italicized*** in the CAEPR (Section 7.1.1).

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

7.3. Expedited Adverse Event Reporting

7.3.1. Expedited AE reporting for this study must use CTEP-AERS (CTEP- Adverse Event Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 7.3.2).

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients. **PLEASE INCLUDE CCCP@COH.ORG ON ALL CTEP-AERS REPORTS SUBMITTED.**

7.3.2. Expedited Reporting Guidelines – CTEP-AERS Reporting Requirements for Adverse Events that occur within 30 Days1 of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

Phase 2 and 3 Trials									
	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
	Unexpected and Expected	Unex-pected	Expected	Unexpected with	Unexpected without	Expected with	Expected without	Unex-pected	Expected

				Hospitali-zation	Hospitali-zation	Hospitali-zation	Hospitali-zation		
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**

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

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

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

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Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

7.4. Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports. Routine Adverse Event Reporting

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

7.5. Secondary AML/MDS

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm. A secondary malignancy is unrelated to the first cancer that was treated, and may occur months or even years after initial

treatment.

CTEP has removed the old AML/MDS forms. Effective August 25, 2010, all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE must be reported via CTEP-AERS. CTCAE v4.0 has three options available to describe treatment-related events:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

8. PHARMACEUTICAL INFORMATION

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

8.1. CTEP-Supplied Investigational Agents

8.1.1. VEGF Trap (NSC 724770)

Other Names: Ziv-aflibercept, AVE0005 **M.W**.: 115 kDa

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

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

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

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

inserted sealing disc, Flurotec® (PTFE) coated.

Preparation: Do not shake VEGF Trap. Withdraw the dose from the vial and further
dilute in 0.9% sodium chloride or 5% dextrose to a final concentration between 0.6 mg/mL and 8 mg/mL.

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

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

> **Caution**: VEGF Trap diluted to a concentration of 0.6 to 8 mg/mL in 0.9% NaCl or 5% dextrose is stable for 8 hours at 25°C in infusion cassettes or IV bags, or up to 24 hours in the refrigerator.

Route of Administration: Intravenous

Method of Administration: Administered VEGF Trap intravenously over 1 hour into a peripheral vein or central venous catheter using an infusion pump; do not exceed an infusion duration of 2 hours. VEGF Trap may be administered using suitable polyvinyl chloride intravenous delivery devices containing DHEP, polyethylene lined PVC, DEHP free PVC containing tris(2-ethylhexyl)trimellitate TOTM; polypropylene, polyurethane, or polybutadiene.
polyolefin intravenous delivery devices; and/or polyethersulfone filters. The infusion
set must contain a 0.2 micron polyethersulfone inline filter (for example, a low protein binding/low drug binding Supor™ Membrane by Pall, or PES membranes by
Millipore). Polyvinylidene fluoride (PVDF) filters or Nylon filters should **not** be used.

8.1.2. Agent Ordering

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

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

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

8.1.3. Agent Accountability

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

8.2. Commercial Agents

8.2.1. Interleukin-2

Other Names: Aldesleukin, IL-2, rlL-2, T-cell growth factor

Classification: Biological response modifier

Mode of Action: Endogenous substance secreted by OK-T4 cells and lymphocytes. Enhances primary and secondary cytotoxic T-cell responses, causes T-cell mitogenesis and proliferation, and enhances non-killer cell activity.

Storage and Stability: Intact vials are stored in the refrigerator (2-8°C) with protection from light. Each vial bears an expiration date.

Reconstituted IL-2 should be further diluted with 5% Dextrose, USP. It is not to be mixed with saline-containing solutions. Reconstituted IL-2 may be diluted as necessary in volumes of 50 ml to 500 ml with 5% Dextrose, USP plus 0.1% Albumin Human, USP. When diluting, the Albumin Human, USP should be added to the 5% Dextrose Injection, USP prior to the addition of the IL-2. When diluted for IV administration in 5% Dextrose Injection, USP, a plastic bag (e.g., Viaflex, manufactured by Travenol Laboratories, Inc.) containing 0.1% Albumin Human. IL-2 is chemically stable for 48 hours at refrigerated and room temperatures, 2-30°C.

Dose Specifics: Interleukin-2 600,000 MIU/kg/dose or 720,000 MIU/kg/dose over 15 minute IV infusion every 8 hours on Days 1-5 of each cycle for a maximum of 14 doses. For the purpose of this study, interleukin-2 will be given at 600,000 MIU/kg.

Preparation: Aseptically inject 1.2 ml of sterile water for injection into the vial to dissolve the lyophilized cake. Since contents of the vial are under vacuum, the diluent should be directed against the sides of the vial to avoid excess foaming. Remove flip-off plastic cap and swab the target area of the stopper with antiseptic.

Administration: For sterility considerations, the reconstituted IL-2 should be administered immediately or held at 2-8°C for up to 12 hours in 1.2 ml of sterile water for injection, and is stable for at least 24 hours at room temperature.

Incompatibilities: Incompatible with normal saline (results in a precipitate). It should not be mixed with anything except D5W and sterile water.

Availability: IL-2 is a FDA approved therapy for melanoma and is commercially available.

Toxicity: See section 7.1.2.

For more information please refer to the drug's package insert.

9. CORRELATIVE/SPECIAL STUDIES

9.1. Laboratory Correlative Studies

All patients participating in the study must undergo correlatives studies. Laboratory correlates will include the following:

- Evaluate baseline serum VEGF level as a predictor for response to this combination regimen to compare the response rates and survival rates between high (greater than 125 pg/ml) and low baseline serum VEGF.
- Measurement of baseline VEGFR2 prior to therapy.
- Measuring VEGF levels prior to and at completion of IL-2 to measure if VEGF remained low throughout the 5 days that IL-2 is administrated.

In addition to these studies listed above, other correlatives studies may be done, utilizing research samples collected on this study, that will primarily focus on biomarkers of prognosis or prediction of therapeutic benefit based on current or future scientific evidence.

9.1.1. Collection of Specimens

Blood specimens will be collected for the purpose of laboratory corollary studies as follows:

Table. Blood sample Collection				
Course 1	**Red Top Tubes[5]**	**Green Top Tubes[6]**	**PAX tubes[7]**	**Yellow Top Tube[8]**
Baseline[1]	3	10	1	1
Cycle 1 of IL-2, Day 1[2]	1	none	none	none
Cycle 1 of IL-2, the day after the last dose of IL-2	1	none	none	none
Cycle 2 of IL-2, Day 1[3]	1	none	none	none
Cycle 2 of IL-2, the day after the last dose of IL-2	3	10	1	none
Course 2/3				none
Week 1[4]	1	none	none	none
Cycle 2 of IL-2, the day after the last dose of IL-2	3	10	1	none
Month 12	3	10	1	none
Progression	3	10	1	none

1. Baseline: within 72 hours of the first dose of aflibercept (Arm A) or IL-2 (Arm B).
2. Cycle 1 of IL-2, Day 1: before both the dose aflibercept and the first dose of IL-2 given on that day. This applies to Arm A only. For Arm B, this time point is not required.
3. Cycle 2 of IL-2, Day 1: before both the dose aflibercept and the first dose of IL-2 given on that day (Arm A) or the first dose of IL-2 (Arm B).
4. Course 2/3, week 1, before the first dose of Aflibercept for arm A and the first dose of IL-2 for arm B
5. 10 cc RED top tubes (BDcat #367820 or SST 367988 gel separator/gold top/ tiger tubes if the center can centrifuge them)
6. 10 cc GREEN top tubes (BD cat # 366480)
7. PAX tube (Fisher #23 021 01)
8. 10 cc YELLOW top tube. (BD cat # 364606)

Transfer or, if applicable, ship blood samples by overnight courier Monday-Thursday only to:

Immunologic Monitoring and Cellular Products Laboratory
University of Pittsburgh Cancer Institute
UPCI-IMCPL, Suite 1.26
Study Coordinator
Hillman Cancer Center
5117 Centre Avenue
Pittsburgh, PA 15213
Tel: (412) 624-0078
FAX: (412) 623-6625

Please submit the Specimen Submission Form (Appendix D) for each sample sent.

Notify the IMCPL study coordinator by fax (412-623-6625) when the samples are shipped. If you are unable to get through to the laboratory by fax, telephone the study coordinator and provide the tracking number.

The IMCPL is the Immunology Core Laboratory for ECOG and has a great deal of experience in shipment and handling of blood, tumor and lymph node samples. The IMCPL provides contact information and a fax request form to the sites, and when a patient is scheduled, a tissue sample kit is shipped (generally via ground) to the site, containing all necessary blood tubes, tumor containers (containing sterile medium) sample instructions as well as return overnight shipping instructions. Upon receipt in the laboratory, the blood and tissue samples are logged in a processed according to the protocol-specific SOPs. Samples which are compromised (hemolyzed or which arrived more than 48 hours after draw/isolation) are discarded (currently less than 2% of >750 samples which arrive at the laboratory annually from ECOG sites).

Pathology Specimen Submissions for Banking for Research Studies (at baseline, then at disease progression):

- Primary Melanoma (for patients with known primary cutaneous melanoma)

  Fifteen (15) unstained slides preferably from the thickest portion of the tumor for immunostains (please do not deparaffinise slides) OR, if the primary pathologist is willing, please request the corresponding block, which will be promptly returned upon request. If the patient has more than one primary lesion, please include above slides and/or block for each primary.

- Resected in-transit or satellite metastases, or cutaneous metastases, or lymph node metastases, or lung metastases

  Fifteen to twenty (15-20) unstained slides from the thickest part of the tumor or, if the primary pathologist is willing, please request the corresponding block, which will be promptly returned upon request.

NOTE: Please provide a surgical pathology report to accompany the slides.

- Progression/Relapse Biopsy (if performed, for banking for future research)

  Fifteen to twenty (15-20) unstained slides from the thickest part of the tumor or, if the primary pathologist is willing, please request the corresponding block, which will be promptly returned upon request.

Please transfer or, if applicable, ship to the IMCPL, as noted above. For shipping, regular mail may be used for these tissue samples OR these may be included in the same package with the blood samples shipped by overnight courier. Also please notify the IMCPL study coordinator as noted above.

9.1.2. VEGF and VEGF R2 Testing

VEGF levels will be tested in serum collected at the following time points:

- Course 1:
  - Baseline: before the first dose of aflibercept (within 72 hours of the first dose of aflibercept) or IL-2 for Arm B patients.
  - Cycle 1 of IL-2, Day 1: before both the dose aflibercept (Arm A) and the first dose of IL-2 given on that day. This applies to arm A only and not required for Arm B.
  - Cycle 1 of IL-2, the day after the last dose of IL-2 (Arms A and B).
  - Cycle 2 of IL-2, Day 1: before both the dose aflibercept (Arm A) and the first dose of IL-2 given on that day (Arms A and B).
  - Cycle 2 of IL-2, the day after the last dose of IL-2 (Arms A and B).
- Courses 2 and 3:
  - Week 1: before the first dose aflibercept for Arm A and the first dose of IL-2 for Arm B.
  - Cycle 2 of IL-2, the day after the last dose of IL-2 (Arms A and B)
- Month 12
- Progression

VEGF R2 levels will be tested only at baseline in both arms.

The standardized R&D Systems ELISA kits for measurement of both VEGF and VEGF-R2. These will be done at the University of Pittsburgh Cancer Institute Immune Monitoring Laboratory (IML). The IMCPL participates in national quality control and comparison surveys and is inspected and accredited by the College of American Pathologists (CAP). It is licensed by DHHS to receive specimens from out-of-state locations (CLIA ID# 39D0657004). The IML is also licensed by the state of Pennsylvania and is inspected by the Pennsylvania Department of Health. The CPL is registered with FDA (#3004571535) for somatic cell culture and tissue processing. It also has a Master File (BB-MF-12244) for the facility operation with FDA.

9.1.3. Banking of Specimens for Future Laboratory Corollary Studies

Specimens will be banked at the IMCPL and additional laboratory corollary studies will be conducted based on the availability of specimens and funding.

9.2. Anti-VEGF Trap Antibody Testing

If a patient experiences a hypersensitivity or infusion reaction to aflibercept, serum should be obtained to evaluate for anti-aflibercept antibody formation at the time of the reaction. At the time of the reaction, whole blood will be collected in red-top

vacutainer tubes (containing no additives or anti-coagulant) for serum preparation using the procedures outlined below. (Schematic diagrams of sample labeling and collection procedures are provided in Appendices F and G).

9.2.1. Serum Sample Collection and Preparation

1. Sample collection: Collect 5 mL of blood in one red top tube (B-D Cat #367814 Hemogard, 5mL plastic tubes with silica clot activator) for each Anti-Aflibercept Antibody sample.
2. Immediately mix by inverting tube at least once.
3. Allow serum to clot for 30 minutes.
4. Centrifuge at 1200 x g for 15 minutes to separate clot from serum.
5. Within 30 minutes after centrifugation draw off serum very slowly with transfer pipette, approaching no closer than 0.5cm of the buffy coat and taking great care not to disturb the buffy coat (any contamination may invalidate the assay).
6. Labels are provided by Regeneron for each specimen. Complete copy with the patient's subject identification number. Place one label on the cryovial (see Appendix F for diagrammatic instructions on label placement) and the second copy on the Sample Shipping Log before transferring the patient sample. Note: for duplicate samples, repeat the labeling step
7. Preparation of serum samples for **Anti-Aflibercept antibody**: Aliquot serum specimen equally into TWO plastic cryovials, one for the primary and one for the duplicate sample. Do NOT exceed 1.5mL of serum into each cryovial; acceptable cryovials are VWR #14224-374 or Corning #430659.
8. Freeze all cryovials as soon as possible. All specimens must be stored frozen at -20° C (or colder) in a freezer that is NOT frost-free, until shipped to the laboratory at Regeneron Pharmaceuticals, Inc. Note: The Sample Freezer Temperature Log must be completed daily.

9.2.2. Serum Sample Shipping

1. Complete the appropriate information for each blood draw on the Sample Shipping Log. Include: subject identification number, and date and time of specimen collection, etc. The original Sample Shipping Log should be kept in the Sample Shipping Log Binder. The Sample Shipping Log pages have been pre-numbered. Use one form per shipment. Begin a new form with each new shipment.

2. Include a **copy** of the Sample Shipping Log with the shipment and send to Regeneron Pharmaceuticals, Inc. at the address below:

Sample Management

Regeneron Pharmaceuticals, Inc.
767 Old Saw Mill River Road
Tarrytown, NY 10591

3. The **original** Sample Shipping Log should be kept in the Sample Shipping Log Binder.
4. **Only the primary samples of each patient should be sent with the first shipment.** This is to ensure that, in case of damage during shipment, there is one sample per subject at the site for the backup. Duplicate samples should be shipped on alternate shipping dates. Please refer to the Shipping Calendar for dates.
5. **Samples should be shipped Monday or Tuesday only.**
6. Sufficient dry ice is to be included for samples to remain frozen for at least 48 hours (we recommend 14 lbs. of dry ice).
7. On the date you will be shipping specimens, please notify Sample Management at Regeneron Pharmaceuticals, Inc. to expect arrival of the box (**914) 345-7644**. Please also fax a copy of the shipping list and FedEx package tracking number to Sample Management at Regeneron Pharmaceuticals, Inc. at (914)-593-1024.
8. Please note that for all shipments you must access the FedEx Ship Manager at www.fedex.com to prepare shipments online. The FedEx Ship Manager provides access to Regeneron's Federal Express account for direct billing purposes. **Prepared shipments that do not utilize the FedEx Ship Manager will NOT be reimbursed. Refer to the FedEx shipping requirements in your Sample Shipping Log Binder for instructions on shipping the samples.**

   Note: It is the Investigator's Responsibility to ensure that all shipments of hazardous/dangerous goods comply with current DOT/IATA regulations.

10. STUDY CALENDAR

These study calendars apply to arm A only. For Arm B (HD IL-2 alone), there are no protocol specific requirements. Study investigators should follow the local institutional standard of care guidelines for safety monitoring and safety laboratory testing on Arm B. Baseline evaluations are to be conducted within 2 weeks prior to administration of protocol therapy on both study arms, unless indicated otherwise, elsewhere in the protocol. Scans and X-rays must be done not more than 28 days prior to the start of therapy on both study arms. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Course 1 (Arm A)	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10
Aflibercept[a]		X		X		X		X		X	
Interleukin-2[a]				X		X					
Informed consent	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	X----------									----------X
Physical exam	X	X		X		X		X		X	
Vital signs	X	X		X		X		X		X	
Blood pressure[h]	X	X	X	X		X		X		X	
Height	X										
Weight	X	X		X		X		X		X	
Performance status	X	X		X		X		X		X	
CBC w/diff, plts Urinalysis and UPCR[b]	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[c]	X	X	X	X	X	X	X	X	X	X	X
PT/INR	X										
Echocardiogram	X										X
Cardiac stress test, ECG[d]	X										
PFTs[e]	X										
Adverse event evaluation		X ----------									----------X
Tumor measurements	X										X
Radiologic evaluation[f]	X										X
B-HCG[g]	X										

a: Aflibercept: IV Day 1 14-day cycle. IL-2: 600,000 U/kg/dose IV Q8h x 5 days (max 14 doses) starting on day 1 of weeks 3 and 5. An IL-2 cycle may be delayed until the resolution of limiting toxicities.

b: Spot urine for protein and creatinine must be obtained to calculate urine protein:creatinine ratio (UPCR). A 24-hour urine collection for quantitative protein determination must be obtained for a UPCR >1.

c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.
d: Patients who are over 40 years old or have had previous myocardial infarction greater than 6 months prior to study entry or have significant cardiac family history (CAD or serious arrhythmias) will be required to have a negative or low probability cardiac stress test (thallium stress test, stress MUGA or exercise stress test) for cardiac ischemia within 8 weeks prior to registration. Patients who are not required to have a cardiac stress test should have an electrocardiogram at baseline to be reviewed by the treating physician investigator. Patients who undergo echocardiography as part of their cardiac stress test are not required to have a separate baseline echocardiogram.
e: Pulmonary function tests (PFTs) are required for patients over 50 years old or with significant pulmonary or smoking history. PFTs may be done up to 4 weeks prior to registration.
f: Radiologic evaluation should include MRI or contrast CT of the brain.
g: Serum pregnancy test (women of childbearing potential).
h: blood pressure will be checked weekly during the first cycle of aflibercept, then every two weeks while on study. However, at the initiation of the maintenance phase, if aflibercept is started at a higher dose than in the combination phase, blood pressure monitoring should be done weekly for the first 3 weeks of the maintenance phase to ensure tolerance of the higher aflibercept dose. This is the minimum blood pressure monitoring required. Appendix H includes a patient diary that includes more frequent blood pressure monitoring and can be used at the discretion of the treating physician.

	Course 2/3 (Arm A)								**Maintenance aflibercept**	
Course 2/3, and Maintenance aflibercept	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8		Off Study[e]
Aflibercept[a]	X		X		X		X		X	
Interleukin-2[a]	X		X							
Concurrent meds	X----------X									
Physical exam	X		X		X		X		X (q 2wks)	X
Vital signs and blood pressure	X		X		X		X		X (q 2wks)	X
Weight	X		X		X		X		X (q 2wks)	X
Performance status	X		X		X		X		X (q 2wks)	X
CBC w/diff, plts Urinalysis and UPCR[b]	X	X	X	X	X	X	X	X	X	X
Serum chemistry[c]	X	X	X	X	X	X	X	X	X	X
Echocardiogram								X		
Adverse event evaluation	X ----------X									X
Tumor measurements								X	X	X
Radiologic evaluation[d]								X	X	X

a: Aflibercept: IV Day 1 of a14-day cycle. IL-2: 600,000 U/kg/dose IV Q8h x 5 days (max 14 doses) starting on day 1 of weeks 3 and 5. An IL-2 cycle may be delayed until the resolution of limiting toxicities. During the maintenance aflibercept phase, aflibercept monotherapy will be initiated to be administered IV on Day 1of each 14-day cycle. In the absence of limiting toxicities, aflibercept will be given at 4 mg/kg in the maintenance phase. In this case, blood pressure monitoring should be done weekly for the first 3 weeks of the maintenance phase to ensure tolerance of the higher aflibercept dose. However, if the aflibercept dose had to be reduced during the combination phase due to aflibercept-related toxicities, then that reduced dose will be used for maintenance therapy. No need for weekly monitoring of blood pressure, if the reduced dose has already been demonstrated to be tolerable.
b: Spot urine for protein and creatinine must be obtained to calculate urine protein:creatinine ratio (UPCR). A 24-hour urine collection for quantitative protein determination must be obtained for a UPCR >1. During the maintenance aflibercept phase, this is to be done every 2 weeks.
c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium. During the maintenance aflibercept phase, this is to be done every 2 weeks.

d: Radiologic evaluation should include MRI or contrast CT of the brain. During the **maintenance aflibercept phase** tumor radiologic evaluation and tumor measurements will take place every 12 weeks (-/+1 week) for the first 2 years, then every 6 months (-/+ 2 weeks) for years 3-5, then yearly (-/+ 4 weeks) afterwards.
e: off study evaluation. Patients will be followed for 5 years after removal from study or until death, whichever occurs first. The frequency and the type of evaluations during this follow up period will follow institutional standard of care practices. For patients who wish not to follow with a study investigator, they can be followed by their treating physician of choice and also following local standard of care practices. Data on disease progression and survival will be collected on all patients every 3-4 months.

For the purposes of this study, patients should be reevaluated for response at the end of course 1 (10 weeks -/+ 1 week for Arm A and 8 weeks -/+ 1 week for Arm B) and at the end of every course thereafter (8 weeks -/+ 1 week). It will be done every 12 weeks -/+ 1 week during the maintenance Aflibercept Monotherapy phase (Arm A) or observation phase (for arm B) for the first 2 years, then every 6 months (-/+ 2 weeks) for years 3-5, then yearly (-/+ 4 weeks) afterwards. Radiologic evaluation should include MRI or contrast CT of the brain on both study arms (A and B).

Off study evaluation for Arm B: Patients will be followed for 5 years after removal from study or until death, whichever occurs first. The frequency and the type of evaluations during this follow up period will follow institutional standard of care practices. For patients who wish not to follow with a study investigator, they can be followed by their treating physician of choice and also following local standard of care practices. Data on disease progression and survival will be collected on all patients every 3-4 months.

11. MEASUREMENT OF EFFECT

11.1. Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be reevaluated for response at the end of course 1 (10 weeks -/+ 1 week for Arm A and 8 weeks -/+ 1 week for Arm B) and at the end of every course thereafter (8 weeks -/+ 1 week). It will be done every 12 weeks -/+ 1 week during the maintenance Aflibercept Monotherapy phase (Arm A) or observation phase (for arm B) for the first 2 years, then every 6 months (-/+ 2 weeks) for years 3-5, then yearly (-/+ 4 weeks) afterwards. Radiologic evaluation should include MRI or contrast CT of the brain on both study arms (A and B). In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1[Eur J Cancer, 2009. **45**(2): p. 228-47.]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

11.1.1. Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first protocol drug administration.

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

NOTE: Since we hypothesize that reducing VEGF will improve response to IL-2, a patient must complete course 1 (at least one cycle of VEGF Trap + 2 cycles of IL-2) in order to be evaluable for response.

11.1.2. Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm with conventional techniques (CT, MRI, x-ray) or as $\geq$10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

11.1.3. Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor 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). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI 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.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

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.

11.1.4. Response Criteria

11.1.4.1. Evaluation of Target Lesions

Complete Response (CR):Disappearance of all target lesions

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

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new

lesions

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

11.1.4.2. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

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

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

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

11.1.4.3. Evaluation of Best Overall Response

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	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: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

11.1.5. Duration of Response

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

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

11.1.6. Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression (or death if there is no progression date). Patients with neither a progression date nor date of death will be censored as of last contact.

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1. Data Reporting

12.1.1. Method

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP web site (http://ctep.cancer.gov). **Note**: **All** adverse events that have occurred on the study, including those reported through CTEP-AERS, must be reported via CDUS.

12.1.2. Responsibility for Data Submission

Study participants are responsible for submitting CDUS data and/or data forms to the
Coordinating Center quarterly by January 31, April 30, July 31, and October 31 to allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP (see Section 12.1.1.). For trials monitored by CTMS, the quarterly data submission to CTEP from provided by Theradex should be copied to the Coordinating Center.

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

12.1.3. Data Collection Forms and Submission Schedule

All data will be collected using COH data collection forms via an electronic data capture system. Any original data collection forms will reside at the originating institutions in secure location.

ELIGIBILITY CHECKLIST: The data manager at the registering site will have completed and faxed this form at the time of registration.
ON-STUDY FORM (FORM OS): Completed on-study forms due within two weeks of registration.
TREATMENT FORM (FORM RX): Completed treatment forms are due within four weeks of completion of a cycle.
ADVERSE EVENT COLLECTION: Completed adverse events collection form due within four weeks of completion of a cycle.
FLOW SHEETS: Protocol specific flow sheets are to be submitted along with each treatment form.
RESPONSE/OFF-STUDY/FOLLOW-UP: Form F/U is to be submitted each time a patient is evaluated for response and/or new follow-up information is obtained.
SUPPLEMENTAL DATA FORM: The timeline for submission of the supplemental data form will be protocol specific, if applicable.

12.2. CTEP Multicenter Guidelines

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

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

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

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

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

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

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

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

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

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

commercialization of its own investigational Agent.

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

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

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

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

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

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

13. STATISTICAL CONSIDERATIONS

13.1. Study Design/Endpoints

This is a randomized Phase II study of HD-IL2 plus aflibercept vs HD-IL2 alone. The randomization is 2:1 in favor of the combination arm, using blocked randomization. The randomization is carried out by the central data coordination center. Stratification is specified in section 13.3, and does not include stratification by center. The primary endpoint is progression-free survival. The accrual goal is 105 (70 patients on the combination arm, 35 patients on the single agent HD-IL2 arm) to be accrued over 2 years, with an additional 6 months of follow-up.

This study design has 89% power to detect a 75% increase in the median PFS (7 vs 4 months), at the 1-sided 0.10 significance level. There are no planned interim analysis other than toxicity considerations due to the possibility that the aflibercept role may be demonstrated in a secondary analysis of the proportion of long-term responders (e.g., >2-yrs).

The primary endpoint of progression-free survival will be measured from data of randomization until date of progression, death, recurrence or censored at last contact. The primary comparison will be based on the log-rank test for comparison of progression-free survival, which will be estimated by the Kaplan-Meier method.

Secondary analysis includes overall survival comparison, one-year survival, response rate, and toxicity. Response rate will be estimated and a 95% CI provided for each arm, and Cox regression will also be conducted for survival and progression-free survival. Survival endpoints will be evaluated from data of randomization, although we will also report on the as-treated populations for comparison.

13.2. Sample Size/Accrual Rate

We plan 24 months of accrual for 105 patients (approximately 4-5 patients per month) and a minimum of 6 months follow-up (no drop outs).

13.3. Stratification Factors

Randomization will be stratified based on the presence or absence of visceral disease, ECOG 0 vs 1, and male vs female. .

13.4. Analysis of Secondary Endpoints

Toxicity Monitoring: HD-IL2 plus Aflibercept arm (Arm A):

Toxicity will be primarily be evaluated by examining the number of doses of HD IL-2 administered during the first cycle of combination therapy; the percentage of patients who receive all 56 doses will also be summarized. The toxicity after the scheduled 10^{th} dose of IL-2, the frequency of grade III and IV toxicities, and unusual toxicities will also be summarized. The toxicity profile for the first six patients enrolled on the

combination arm after the first cycle of high dose IL-2 will be reviewed by PI, the treating physician or local PI at each of the enrolling institutions, the statistician, and the senior investigator at the NCI/CTEP in a conference call. Approval for continuing the trial will require a majority consensus to continue in addition to requiring approval from the PI and the NCI senior investigator.

For safety reasons, accrual to the study will initially be staggered by at least a week for the initial 3 patients. In addition, toxicity profile will be assessed for each of two cohorts of 3 patients after the initial 5 weeks of therapy. If no unexpected toxicity or death occurs, the next cohort of three patients will be allowed to enter the trial. The same toxicity review will occur for cohort 1 as at the end of cohort 2 (see above). If approval is obtained, accrual will be allowed to proceed to the second toxicity analysis point of 19 patients.

After 19 patients have initiated and completed their first cycle of therapy, an analysis of toxicity will be undertaken. Among the initial 15 patients treated with high dose IL-2 and aflibercept, there is high probability of observing rare toxicities if they exist: there is probability of 0.62 of observing at least one event that occurs at a true rate of 5%; and probability of 0.86 of observing at least one event that occurs at a true rate of 10%. This review will also be conducted with same oversight described above at the 6 patient time point. An additional review will be mandated upon any treatment-related death, and every 6 months.

Based on previous experience with high dose IL2 at the University of Pittsburgh, the median number of doses per course 1 (first 2 cycles) as monotherapy[22] is 16 (range 8-26) and in sequential combination with temozolomide[23] is 15 (range 7-23). As a result, the median number of doses per course 1 will be considered in addition to toxicity reported via CTCAE criteria.

Among all 70 patients treated with combination therapy, there is probability of 0.51 of observing at least one event that occurs at a true rate of 1%; and probability of 0.97 of observing at least one event that occurs at a true rate of 5%.

Correlative Endpoints:

If the agent is promising, we expect to have 70 patients to evaluate for correlative science on the combination arm. We expect all patients to provide measurements of serum VEGF levels and other blood-based biomarkers, with a subset with corresponding tissue related correlatives. Previous data has suggested that high VEGF levels predict lower response to IL-2, With a minimum expected balance of 16 (responders) vs 54 (non-responders), there will be a minimum of 96% power to detect a one standard deviation difference (after aflibercept therapy) in the VEGF levels in responders vs non-responders, with a one-sided type I error of 0.05 (NOTE: we expect at least 16 responders out of the 70 patients evaluable for correlative science on the combination arm. If more are obtained, the statistical operating characteristics improve due to better balance between responders and non-responders). We will also compare

the mean baseline VEGF levels in responders and non-responders and provide a 95% confidence interval as part of our exploratory analysis.

Correlative endpoints will also be explored using multivariate Cox regression, exploring the impact of both baseline VEGF levels and VEGF levels after aflibercept therapy, while adjusting for known patient characteristics that impact survival.

Other correlative endpoints will also be explored, including evaluating the biological correlatives in the HD-IL2 alone arm, and while no attempt will be made to adjust for multiple comparisons for additional correlative endpoints, any conclusions will be stated as exploratory and in the context of a randomized phase II study.

13.5. Reporting and Exclusions

13.5.1. **Evaluation of toxicity.** All patients will be evaluable for toxicity from the time of their first treatment.

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

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

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

14. CCCP POLICIES FOR MONITORING CONSORTIUM TRIALS

The protocol principal investigator (PI) is responsible for monitoring the conduct and progress of this Phase I trial, including the ongoing review of accrual, data and toxicities,

as well as the accumulation of reported adverse events from other trials testing the same drug(s). The participating clinicians and their designees are responsible for timely submission of adverse event reports (see Section 7.0) and case report forms. The Data Coordinating Center for the CCCP Consortium is responsible for providing the PI with access to the submitted case report form data in summary and detail in a timely fashion. Although the PI is responsible for evaluating the cumulative reported adverse events and the impact that these have on the continued conduct of the trial, it is the Data Coordinating Center of the CCCP that distributes all submitted SAE reports to the appropriate individuals, including the local protocol principal investigators, at each of the participating institutions.

The Data Coordinating Center posts a summary (accrual, toxicities, and responses) of each CCCP initiated trial on the CCCP website. In this way, each PI has access to up-to-date information on the status of his or her trial. In consultation with the collaborating statistician, the PI is responsible for review of:

(a) for Phase I trials, all dose limiting toxicities and decisions regarding dose escalation, expansion, as well as decisions to terminate escalation, and
(b) for Phase II trials, the toxicities and therapeutic endpoints referred to in the statistical plan.

The Data Coordinating Committee meets monthly to review data management and data quality issues – completeness of data submissions as well as accuracy in terms of built-in, computerized logic checks. Any issues identified and the corrective plans are presented to the Internal Committee and at the next CCCP teleconference meeting for review and approval.

Oversight
Oversight of the conduct of CCCP trials occurs at several levels:

1. The Data Coordinating Center for the CCCP flags all trials that are approaching a decision in terms of toxicity (for both Phase I and Phase II trials) or responses (for Phase II trials). Decisions are made by the PI with input from the statistician and discussion with the principal investigator of the funding mechanism (U01 Cooperative Agreement or N01 Contract, as appropriate) or his or her designee, and are communicated to the participating centers by the CCCP Data Coordinating Center. At the monthly teleconferences, the accrual of each open protocol is reviewed.

2. For CTEP sponsored Phase I trials, data are reported to the NCI-designated clinical trials monitoring service (CTMS) which will audit patients' records on each protocol – at each CCCP institution; this audit is initiated by CTEP. For all other CCCP trials, the CCCP will contract with Theradex to audit patient records at each CCCP institution.

3. An independent CCCP DSMC will review CCCP trials every 6 months. This DSMC will consist of 3 voting members (2 medical oncologists or hematologists involved in Phase I/II cancer clinical trials but not participating in CCCP studies, and a statistician) and a non-voting CCCP statistician.

   a. DSMC meetings will take place twice a year. Additional meetings will be convened if necessary.
   b. This DSMC will review each CCCP trial in terms of accrual, toxicity/safety, and adherence to trial design, audit results, and likelihood of successful completion.
   c. The DSMC will report to the CCCP leadership.

15. REFERENCES

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APPENDIX A – Performance Status Criteria

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

APPENDIX B – CTEP Multicenter Guidelines

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

Responsibility of the Protocol Chair

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

Responsibilities of the Coordinating Center

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

Inclusion of Multicenter Guidelines in the Protocol

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

Agent Ordering

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

APPENDIX C – CCCP Registration Procedures for Phase II Trials

1. Registrations for Phase II protocols must be made through the California Cancer Consortium office at the City of Hope between the hours of 8:30 a.m. to 4:30 p.m., Monday through Friday (except holidays).

2. Patients must be registered within 3 days prior to initiation of protocol therapy.

3. A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, contact the City of Hope Data Coordinating Center (DCC) at (626) 256-HOPE (4673), ***extension 65928.***

4. Prestudy laboratory tests, scans and x-rays must be completed prior to registration according to study calendar/protocol.

5. Patients must sign an informed consent prior to registration.

6. Confirm that the patient meets all inclusion and exclusion eligibility criteria for a protocol.

7. Complete the Eligibility Checklist.

8. Verify that all required prestudy tests were performed.

9. Fax the completed Eligibility Checklist, signed and dated informed consent, pathology report, and relevant laboratory results to the City of Hope Consortium Coordinator for confirmation of eligibility. The FAX number is (626) 256-8654.

10. Call the City of Hope Consortium Coordinator at (626) 256-HOPE (4673), extension 65928 to confirm the FAX arrival. If the Consortium Coordinator is not in the office, have them paged at (626) 423-5365.

11. If the patient qualifies, the City of Hope Consortium Coordinator will call the registering institution to complete the registration/randomization procedure and assign the patient's study ID number.

12. Once a patient has been registered, the Data Coordinating Center will provide a "Confirmation of Registration" to the center registering the patient.

For questions regarding eligibility call City of Hope California Cancer Consortium, Data Coordinating Center
(626) 256-HOPE (4673), extension 65928

APPENDIX D – CCCP Specimen Submission Forms

Please contact the Data Coordinating Center at cccp@coh.org for the CCCP Specimen Submission Form. The form will be emailed to the participating institution when the study has been activated.

An additional form called "PhII-107 Research Specimen Submission Form" will also need to be completed and will be distributed to activated. If a copy is needed, please contact the DCC at cccp@coh.org.

APPENDIX E – NYHA functional classification system

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

APPENDIX F - Labeling Instructions for Serum Samples for Regeneron (Anti-Aflibercept Antibody Testing)

1. Verify that the number directly under the Barcode on the label to be affixed to the vial matches the corresponding label to be affixed to the shipping paperwork.

2. Complete the information required on the visit-specific label: Subject ID. Please note that you will need to complete the following additional fields if you are using an Unscheduled Visit Label: Visit #, Date, Time, and Sample Type (serum or plasma).

Visit-Specific Specimen Label

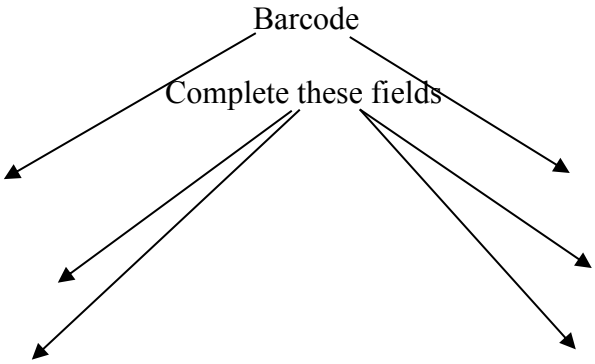
REGENERON
Pharmaceuticals, Inc

SAG
VEGFT-RA-0402-
00100004

Subject ID _ _ _ _ _ _

__

Visit 1, Timepoint:



Unscheduled Visit Specimen Label

REGENERON
Pharmaceuticals, Inc

SAG
VEGFT-RA-0402-
00100004

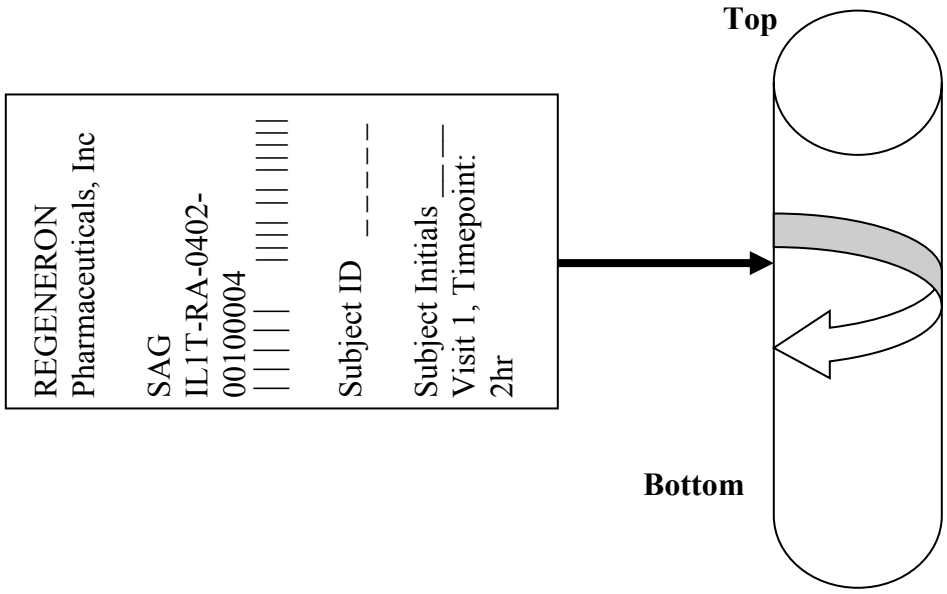
Subject ID _ _ _ _ _ _

__

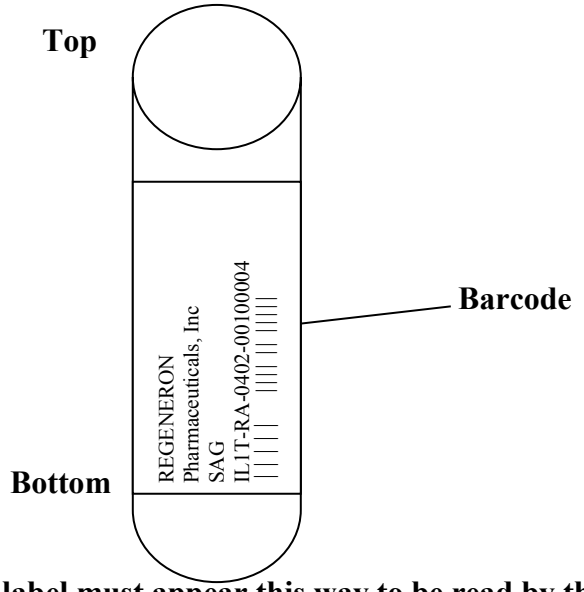
Visit #

3. Remove label from backing, turn label sideways (to the left), and apply the bottom of the label to the cryovial first. Make sure that the label does not cover the threading on the top of the cryovial. Wrap remaining portion of label in a clockwise direction around cryovial and be sure that the label's bar code runs vertically along the cryovial. Please refer to the picture of correctly labeled cryovial on next page.

1.8 mL cryovial



Correctly Labeled Cryovial with Barcode in Vertical Direction



Please note that the label must appear this way to be read by the label scanner.

WHAT TO DO IN CASE OF MISTAKES

If you accidentally used the wrong label for a cryovial, please:

- Remove the incorrect label and re-label the cryovial with the correct label. If you do not have an extra label for a particular visit, you should use an **Unscheduled Visit Label** and complete the required information. Please save the incorrect label and attach it to the shipping list with a written explanation of the error.

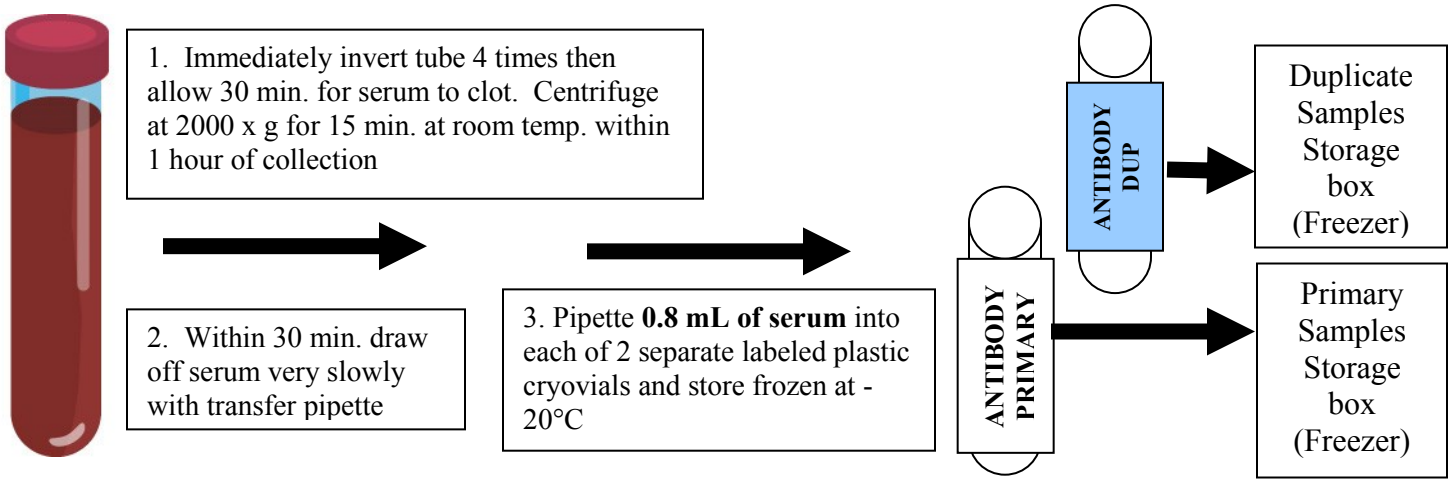
If you made a mistake on the label, such as writing the wrong subject initials or date, please:

- Cross out the wrong information and write the correct information on the label. Make sure that you initial and date the cross-out. If you cannot correct the label in a legible fashion, use an Unscheduled Visit Label (see top of Page 1).

APPENDIX G - COLLECTION OF SERUM SAMPLES for Regeneron (Anti-Aflibercept Antibody Testing)

SERUM Samples for Regeneron

Anti-VEGF Trap Antibody Samples



5 mL plain red top tube 2 cryovials with **0.8 mL serum** each

Note: 1. Collect one red top tube for each sample.

2. Only one cryovial per subject per time point should be sent with the initial scheduled shipment.

3. Refer to SERUM Sample Collection and Preparation instructions for additional details.

APPENDIX H - Patient Blood Pressure Monitoring Diary (for patients on Arm A receiving Aflibercept)

NOTE: This optional diary is strongly recommended to be used as more frequent blood pressure monitoring than what is required in the protocol and can be used at the discretion of the treating physician.

Diary Card
Blood Pressure Monitoring

Dates: ____/____/____ to ____/____/____

Patient Number: Patient Initials:

Hypertension is a known and potentially serious adverse event associated with aflibercept treatment. It is recommended that you have your blood pressure monitored as follows:

- At least twice weekly during the first 5 cycles of aflibercept therapy (Course 1 of protocol therapy) and prior to each infusion of aflibercept.
- At least once weekly during each subsequent cycle of aflibercept therapy.
- If the blood pressure is not well controlled, then it should monitored more frequently.

Blood pressure is typically recorded as two numbers, written as a ratio. The top number (systolic), which is also the higher of the two numbers, measures the pressure in the arteries when the heart beats (when the heart muscle contracts). The bottom number (diastolic), which is also the lower of the two numbers, measures the pressure in the arteries between heartbeats (when the heart muscle is resting between beats and refilling with blood).

You should contact your physician's office if your blood pressure exceeds 140 mmHg (systolic) or 90 mmHg (diastolic) at any time and are encouraged to contact your physician if you are concerned about any symptoms that may be associated with high blood pressure (*e.g.*, headache).

You should seek **immediate** medical advice if your blood pressure exceeds 180 mmHg (systolic) or 105 mmHg (diastolic) at any time and are encouraged to contact you physician if they are concerned about any symptoms that may be associated with high blood pressure (*e.g.*, headache).

While you are receiving treatment with aflibercept, the early initiation of antihypertensive treatment to minimize more severe or persistent hypertension is considered an important precautionary measure to avoid potentially serious complications.

When you are receiving IL2 on Arm A, the blood pressure medications should be managed as follows:

- On the day of admission, the morning blood pressure medications should be taken, anticipating that the first dose of IL2 is given that evening. Otherwise, if the first dose of IL2 is expected to be given during the day, then the morning blood pressure medications should be held.
- If the first dose of IL2 is anticipated to be given in the evening of the day of admission, then the blood pressure medications should be held for that evening and throughout IL2 treatment unless otherwise specified by the treating physician

- Upon completion of IL2 therapy, the blood pressure medications should restarted as soon as the IL2 induced hypotension (low blood pressure) has resolved. Most importantly, the blood pressure medications should be restarted before the patient is discharged home.
- Following home discharge from inpatient IL2 therapy, you should have the blood pressure monitored at least twice weekly and contact your physician's office if your blood pressure exceeds 140 mmHg (systolic) or 90 mmHg (diastolic) as noted above.

Blood Pressure No.	Date						TIME Record Time of Blood Pressure (Circle AM or PM)			Use the space below to make notes about things you would like to tell the doctor (include any unusual symptoms you experience, other medicine you have taken and anything else you think may be of interest.
	Month		Day		Year		BP	TIME	circle AM/PM	
1								:	AM PM	
2								:	AM PM	
3								:	AM PM	
4								:	AM PM	
5								:	AM PM	
6								:	AM PM	
7								:	AM PM	
8								:	AM PM	
9								:	AM PM	
10								:	AM PM	
11								:	AM PM	
12								:	AM PM	
13								:	AM PM	
14								:	AM PM	
15								:	AM PM	
16								:	AM PM	
17								:	AM PM	
18								:	AM PM	
19								:	AM PM	
20								:	AM PM	
21								:	AM PM	
22								:	AM PM	
23								:	AM PM	
24								:	AM PM	
25								:	AM PM	
26								:	AM PM	
27								:	AM PM	
28								:	AM PM	
29								:	AM PM	
30								:	AM PM	