Amendment

Protocol Number: 14C0150-E **Reference Number:** 367158

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Protocol Title: Phase I Study of Ganetespib and Ziv-Aflibercept in Patients with Advanced Gastrointestinal Carcinomas, Non-Squamous Non-Small Cell Lung Carcinomas, Urothelial Carcinomas, and Sarcomas

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* Signature signifies that investigators on this protocol have been informed that the collection and use of personally identifiable information at the NIH are maintained in a system of record governed under provisions of the Privacy Act of 1974. The information provided is mandatory for employees of the NIH to perform their assigned duties as related to the administration and reporting of intramural research protocols and used solely for those purposes. Questions may be addressed to the Protrak System Owner.

** I have reviewed this research project and considered the NIH Policy for Inclusion of Women and Minorities in Clinical Research. Taking into account the overall impact that the project could have on the research field involved, I feel the current plans adequately includes both sex/gender, minorities, children, and special populations, as appropriate. The current enrollment is in line with the planned enrollment report for inclusion of individuals on the basis of their sex/gender, race, and ethnicity and is appropriate and of scientific and technical merit.

IRB Meeting Date: N/A

DEC Clearance Date: N/A

Protocol Version Date: 02/13/2017

TITLE: Phase I Study of Ganetespib and Ziv-aflibercept in Patients With Advanced Gastrointestinal Carcinomas, Non-Squamous Non-Small Cell Lung Carcinomas, Urothelial Carcinomas, and Sarcomas

Abbreviated Title: Ph I Ganetespib Ziv-aflibercept

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NCI Supplied Agent:	Ganetespib (NSC 777169) Ziv-aflibercept (NSC 724770) ^{89}Zr-Labeled, EGFR-targeting Antibody Panitumumab (supplied by CIP/DCTD)
IND Number:	123037
Version Date:	February 13, 2017

Roles: A obtains information by intervening or interacting with living individuals for research purposes; B obtains identifiable private information about living individuals; C obtains the voluntary informed consent of individuals to be subjects; D makes decisions about subject eligibility; E studies, interprets, or analyzes identifiable private information or data/specimens for research purposes

PRÉCIS

Background:

- Ganetespib is a non-geldamycin synthetic inhibitor of Hsp90 that has demonstrated activity against multiple cancer cell lines and tumor xenografts. Inhibiting the Hsp90 chaperone complex results in the recruitment of ubiquitin ligases, polyubiquination, and proteosomal degradation of Hsp90 client proteins, including transcription factors and proteins involved in angiogenesis (VEGF, VEGFR, HIF-1, STAT-3); growth factor independence (RAF, EGFR, Her2, IGFR); resistance to anti-growth signals (CDK4); tissue invasion and metastases (MET, MMP2); and avoidance of apoptosis (AKT, RIP, Survivin, Bcl-2).
- HIF-1α activation has been implicated in mediating resistance to anti-angiogenic therapy; recent evidence implicates a greater role for Hsp90 in direct modulation of VEGF signaling
- Combining Hsp90 inhibition with ganetespib and anti-angiogenic therapy with ziv-aflibercept, a soluble fusion protein with high binding affinity for VEGF-A, VEGF-B, and PIGF, presents a novel rational strategy for improving on and overcoming resistance to anti-angiogenic therapy

Primary Objective:

- To establish the safety, tolerability, and maximum tolerated dose (MTD) of the combination of ganetespib and ziv-aflibercept in patients with refractory gastrointestinal carcinomas, non-squamous non-small cell lung carcinomas, urothelial carcinomas, and sarcomas

Secondary Objectives:

- To assess modulation of HIF1α as a pharmacodynamic marker of therapy with the combination of ganetespib and ziv-aflibercept
- To assess modulation of EGFR expression using ^{89}Zr-labeled, EGFR-targeting antibody panitumumab PET/CT imaging of tumor lesions prior to and following treatment with study drugs

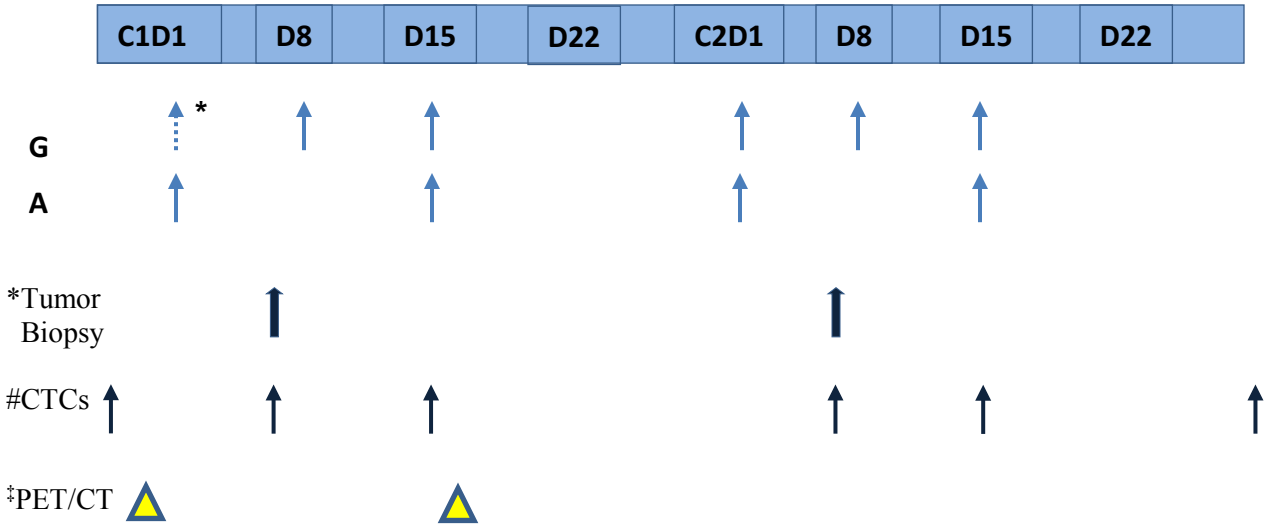
Eligibility:

- Adult patients with histologically confirmed metastatic gastrointestinal carcinomas, non-squamous non-small cell lung carcinomas, urothelial carcinomas, and sarcomas with disease progression after at least one line of standard therapy
- Participants in the expansion phase must demonstrate EGFR expression on archival tumor samples and have disease amenable to biopsy with willingness to undergo pre- and post-treatment biopsies
- No major surgery within 4 weeks prior to study enrollment, no radiation or chemotherapy within 3 weeks prior to enrollment; patients must have recovered from toxicities of prior therapies to at least eligibility levels prior to enrollment.

Study Design:

- Ganetespib will be administered IV weekly on days 1, 8, and 15 of a 28-day cycle. Ziv-aflibercept will be administered IV on days 1 and 15 of a 28-day cycle.
- The escalation portion of the trial will follow a standard 3+3 design, whereby patients are dose-escalated in cohorts of 3 until dose-limiting toxicity is observed.
- Once the MTD is established, 10 additional patients will be enrolled to the expansion phase at the MTD, and tumor biopsies will be obtained to assess pharmacodynamic endpoints. During cycle 1 of the expansion phase, ganetespib will be administered IV weekly, on days 8 and 15 with omission of day 1 treatment to accommodate a baseline biopsy pre-ganetespib but after administration of ziv-aflibercept. For all subsequent cycles, ganetespib will be administered days 1, 8, and 15. Ziv-aflibercept will still be administered IV on days 1 and 15 of a 28-day cycle.
- PET/CT imaging with ^{89}Zr-labeled panitumumab will be performed to evaluate tumor distribution prior to and following treatment with study agents.

SCHEMA



G = Ganetespib
A = Ziv-aflibercept

* Tumor biopsies (optional during the escalation phase, mandatory during the expansion phase) will be performed on C1D7 prior to administration of ganetespib on C1D8 and again on C2D7 prior to administration of ganetespib on C2D8. If tumor biopsies are pursued, the first dose of ganetespib on C1D1 will be omitted.

#Circulating tumor cells (optional) will be collected during the expansion phase only at baseline (pre-treatment), on C1D8 (+/- 1 day) prior to the administration of ganetespib, on C1D15 4 hours (+/- 1 hour) after completion of drug administration, on C2D8 (+/- 1 day) prior to the administration of ganetespib, on C2D15 4 hours (+/- 1 hour) after completion of drug administration, on day 1 of all subsequent cycles before drug administration, and at disease progression.

‡ ^{89}Zr-panitumumab PET/CT imaging will be performed in all patients during the expansion phase (optional during the escalation phase), prior to initiation of treatment. If there is evidence of measurable uptake on baseline scans, patients will receive a second scan on C1D16 day to assess for evidence of EGFR target modulation. If patients are unable to have a second scan on C1D16 $\pm$ 1 day due to scheduling conflicts, scans may be done on C2D16 $\pm$ 1 day.

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1 OBJECTIVES

Primary Objective:

- To establish the safety, tolerability, and the maximum tolerated dose of the combination of ganetespib and ziv-aflibercept in patients with refractory gastrointestinal carcinomas, non-squamous non-small cell lung carcinomas, urothelial carcinomas, and sarcomas

Secondary Objectives:

- To assess the modulation of HIF1α as a pharmacodynamic marker of therapy with the combination of ganetespib and ziv-aflibercept

- To assess modulation of EGFR expression using ^{89}Zr-labeled, EGFR-targeting antibody panitumumab PET/CT imaging of tumor lesions prior to and following treatment with study drugs as an exploratory non-invasive evaluation of Hsp90 client protein modulation

2 BACKGROUND

2.1 Role of Hsp 90 chaperone in Angiogenesis and Cancer

Induction of angiogenesis is one of the hallmarks of carcinogenesis; malignant tumors are dependent upon angiogenesis for oxygen support, growth, and metastasis [1]. The central driving force behind angiogenesis is the interaction of pro-angiogenic signaling pathways with various endothelial cell signaling pathways. Additionally, more recent evidence also implicates a role for the co-optation of cells in the tumor microenvironment for additional tumor support and progression [2]. The development of anti-angiogenic agents has brought to light new resistance mechanisms invoked by both tumor cells as well as cells in the tumor microenvironment, leading to the idea that simultaneous targeting of multiple resistance pathways will enhance anti-tumor activity.

Hsp90 is a molecular chaperone involved in the folding and stabilization of newly synthesized or misfolded proteins, and accordingly involved in many signaling pathways important for tumor cell survival, proliferation, and metastasis [3]. More than 100 individual Hsp90 client proteins have been identified. These include transcription factors and proteins involved in angiogenesis (VEGF, VEGFR, HIF1, STAT-3); growth factor independence (RAF, EGFR, HER-2, IGFR); resistance to anti-growth signals (CDK4); tissue invasion and metastases (MET, MMP2); and avoidance of apoptosis (AKT, RIP, Survivin, Bcl-2). Hsp90 inhibition results in ubiquination and proteosomal degradation of misfolded client proteins, providing an opportunity for effecting antitumor activity through inhibition of multiple oncogenic pathways.

Extensive preclinical and clinical evidence supports the hypothesis that exposure to anti-angiogenic therapy can, paradoxically, cause an adaptive-evasive response with induction of local invasiveness and distant metastases [4]; HIF1α has been implicated in mediating

this response and inducing resistance to anti-VEGF therapy [5]. Preclinical models in sarcomas confirm synergism of anti-VEGF inhibition and HIF1α-inhibition [6]. Based on recent evidence implicating a greater role for Hsp90 in angiogenesis, with direct modulation of VEGF signaling, vessel formation [7], and stabilization of the HIF1α dimerization complex required for Raf/Mek/Erk-mediated endothelial cell proliferation [8], the combination of Hsp90 inhibition with ganetespib and an anti-angiogenic agent such as ziv-aflibercept, present a rational novel strategy for improving upon and overcoming resistance to the inhibition of angiogenesis.

Ganetespib is a non-geldamycin Hsp90 inhibitor which exerts its action by binding to the ATP pocket in the N-terminus of Hsp90. Preclinical studies demonstrate potent Hsp90 inhibition in multiple tumor models including colon, lung, and breast [9-12]. Ziv-aflibercept is a soluble fusion protein comprised of the immunoglobulin domain of VEGFR1 and VEGFR2 fused to the Fc portion of human IgG1. It acts as a high-affinity soluble VEGFR decoy receptor, and has high affinity for VEGF-A, VEGF-B, and PIGF. VEGF is central to endothelial cell survival and promotion of angiogenesis; PIGF is a chemotactic factor of endothelial cells and has been implicated in the mobilization of bone marrow-derived progenitor cells and response to VEGF-induced angiogenic signaling [13].

Rationale for Combination of Ganetespib and Ziv-aflibercept in Gastrointestinal Carcinomas:
Epidermal growth factor receptor is a member of the ErbB family of receptors, and its expression is found in an estimated 60-80% of colorectal cases [14]. Events downstream of the EGFR pathway have been implicated in colon carcinogenesis, and include Ras-mediated activation of the PI3K/Akt/mTOR and Raf/Mek/Erk pathways. EGFR-mediated activation of the PI3K/Akt/mTOR pathway has also been implicated in upregulation of HIF1α and VEGF [15]. Additionally, both Akt and Raf are known client proteins modulated by Hsp90. In vitro evidence supports antiangiogenic modulation by ganetespib in colorectal cancer cells, where significant inhibition of HIF1α and STAT-3 in addition to PDGFA, FGF2, Ang-1, Ang-2, TGFβ1, and VEGF were observed in both KRAS wild-type and mutant cell lines. Downregulation of mRNA transcripts for the same angiogenic factors previously mentioned were also seen in ganetespib-treated tumor samples [16]. Antiangiogenic therapy with ziv-aflibercept is currently approved for use in patients with metastatic colorectal cancer [17].

Rationale for Combination of Ganetespib and Ziv-aflibercept in Lung Carcinomas:
Extensive preclinical evidence exists for antitumor activity of Hsp90 inhibition in non-small cell lung cancer (NSCLC) [18, 19]. Ganetespib has also previously been tested in combination with bevacizumab in preclinical models of NSCLC, with evidence of enhancement of in vitro and in vivo efficacy [16]. Based on results of the Phase 3 ECOG 4599 trial [20] and AVAiL trial [21], bevacizumab is currently approved for the initial systemic treatment of patients with metastatic NSCLC. A recent multicenter Phase 2 study of ganetespib in advanced non-small cell lung cancer has demonstrated significant single agent activity [22]. In this study, PFS rates at 16 weeks were 13.3% in patients with EGFR mutation, 5.9% in patients with KRAS mutation, and 19.7% in patients who had neither

mutation. The combination of Hsp90 inhibition, with ganetespib, and anti-angiogenic inhibition, with ziv-aflibercept, allows for enhancement of antitumor efficacy.

Rationale for Combination of Ganetespib and Ziv-aflibercept in Urothelial Carcinomas:
EGFR and HER2/neu, both Hsp90 client proteins, are highly expressed in urothelial carcinoma cells and expression correlates with stage, grade, and survival [23, 24]. In case series studied, HER2/neu expression and amplification correlated with survival both alone and when co-expressed with other EGFR family members; median survival for those with HER2/neu-expressing tumors was 33 months compared with 50 months in HER2/neu-non-expressing tumors [25]. Early preclinical data with the EGFR inhibitor cetuximab demonstrated a dose-dependent decrease in cell proliferation of the malignant urothelial cell line 253J [26]. Additionally, HIF1α overexpression has been implicated as a predictor of tumor recurrence and progression in urothelial carcinomas [27]. The combination of Hsp90 inhibition, with ganetespib and anti-angiogenic inhibition, with ziv-aflibercept, allows for the targeting of multiple poor-prognostic pathways, and amplification of antitumor activity.

Rationale for Combination of Ganetespib and Ziv-aflibercept in Sarcomas:
Angiogenesis is crucial to the growth and dissemination of sarcomas. Microarray profiling of soft tissue sarcomas demonstrated 10-fold higher levels of VEGF compared to normal tissues controls [28]. More recent studies demonstrated a role for upregulation of HIF1α as a mechanism of resistance of soft tissue sarcomas to antiangiogenic therapies, and that inhibition of HIF1α can augment the destruction of tumor vasculature within sarcoma xenografts [29]. In addition to VEGF, overexpression of many receptor tyrosine kinases has also been implicated in the pathogenesis of soft tissue sarcomas, including HER2 and IGF-1R, both are client proteins of Hsp90 [30]. Recent proteonomic analyses of osteosarcomas also show overexpression of Hsp90 in all osteosarcomas, and 30 of 75 high-grade sarcomas analyzed [31].

2.2 Ganetespib

Mechanism of Action
Ganetespib is a non-geldamycin inhibitor of Hsp90 chaperone activity, exerting activity through binding at the N-terminal adenosine triphosphate (ATP) pocket of Hsp90, and inhibiting its function. Hsp90 inhibition causes its client proteins to adopt aberrant conformations, which are then targeted for ubiquination and proteosomal degradation. Client protein degradation results in induction of cell cycle arrest and apoptosis, thereby inhibiting tumor growth [9]. Ganetespib has activity against a broad spectrum of cancer cell lines compared to first generation Hsp90 inhibitors [32] with an average IC50 value 20-fold lower than 17-AAG [9].

Preclinical Studies

In Vitro Studies

Reverse Phase protein arrays performed on lysates from four KRAS mutant NSCLC cell lines treated with for 24 hours show diminished expression of multiple receptor kinases (including EGFR, MET, HER2), signaling intermediates (CRAF, Src, STAT3, MAPK, GSK3), kinases involved in protein synthesis and growth (AKT/mTOR), resulting in the activation of apoptotic mediators and cell cycle arrest [33].

Function	Analyte	Cell Lines			
		H2009	A549	H358	Calu-1
AKT/mTOR	S6 (pS235/S236)	-9.1	-6.3	-27.2	-7.5
	S6 (pS240/S244)	-9.2	-7.5	-22.4	-9.8
	AKT (pS473)	-2.0	-2.0	-1.7	-1.1
	4E-BP1 (pS65)	-1.3	-1.7	-4.2	-1.7
	AKT	-1.8	-1.7	-1.8	-3.0
	mTOR (pS2448)	-1.9	-1.3	-1.9	-2.3
	PDK1 (pS241)	-1.6	-1.9	-1.4	-1.8
	p70S6K	-1.5	-1.6	-1.3	-1.9
	Tuberin	-1.8	-1.4	-1.5	-1.5
MAPK	C-RAF (pS338)	-2.7	-2.3	-2.8	-1.9
	C-RAF	-2.1	-2.8	-2.3	-2.4
	EphA2	-1.6	-1.6	-2.1	-1.7
	MAPK (pT202/Y204)	-1.7	-1.4	-1.5	-1.5
	MEK1 (pS217/S221)	-1.1	-1.1	-1.5	-2.4
ATP/metabolism	ACC (pS79)	-2.0	-1.8	-2.7	-4.4
Cell Cycle	CHK1	-1.4	-1.4	-1.7	-1.6
	Cyclin E1	-1.4	-1.6	-1.5	-1.4
Other	GSK3 (pS9)	-1.6	-1.9	-2.6	-2.8
	Src (pY416)	-4.0	-2.0	-2.2	-3.0
	GSK3-A/B (pS21S9)	-1.6	-1.6	-1.7	-1.8
	Src (pY527)	-2.2	-1.6	-1.5	-2.5
	STAT3 (pY705)	-2.8	-1.4	-1.7	-2.2
	GSK3-A/B	-1.6	-1.3	-1.3	-1.4
RTK	EGFR (pY1068)	-14.1	-1.6	-1.6	-1.7
	HER2 (pY12480	-5.5	-1.7	-1.9	-1.6
	IGF-1R □	-1.8	-1.5	-2.0	-1.7
	c-Met (pY1235)	-10.9	1.0	1.1	-1.1
	HER2	-3.2	1.6	-1.9	-1.9
	EGFR	-1.2	-1.3	-1.1	-1.3
Apoptosis/Arrest	Annexin I	1.1	1.1	1.4	1.6
	Caspase 7 (cleaved)	1.4	1.4	1.2	1.3
	p21	1.4	1.1	1.3	2.0
	Cyclin B1	1.5	2.2	1.2	1.1
	BIM	1.7	1.3	1.5	2.5
Stress	HSP70	2.4	2.4	2.6	2.4

Table 1. Fold-changes in protein expression following Ganetespib Treatment (250 nM, 24 hours) in KRAS- Mutant NSCLC Lines.

In Vivo Studies

Pharmacodynamic analyses were performed in mice bearing H3122 xenografts, a non-small cell lung carcinoma model with constitutively active ELM4-ALK fusion kinase. Animals were treated with a single-bolus injection of ganetespib (50 mg/kg) and tumors were harvested at 24, 48, 72, and 96 hours. For comparison, animals were treated with a single injection of vehicle or crizotinib (50 mg/kg) and tumors were collected at 24 hours. Levels of Hsp90 client proteins were evaluated by immunoblotting, namely ERK, MET, EGFR, pSTAT3, and pAKT, and all showed evidence of degradation detectable at 24 hours, and lasting up to 72 hours (Figure 1).

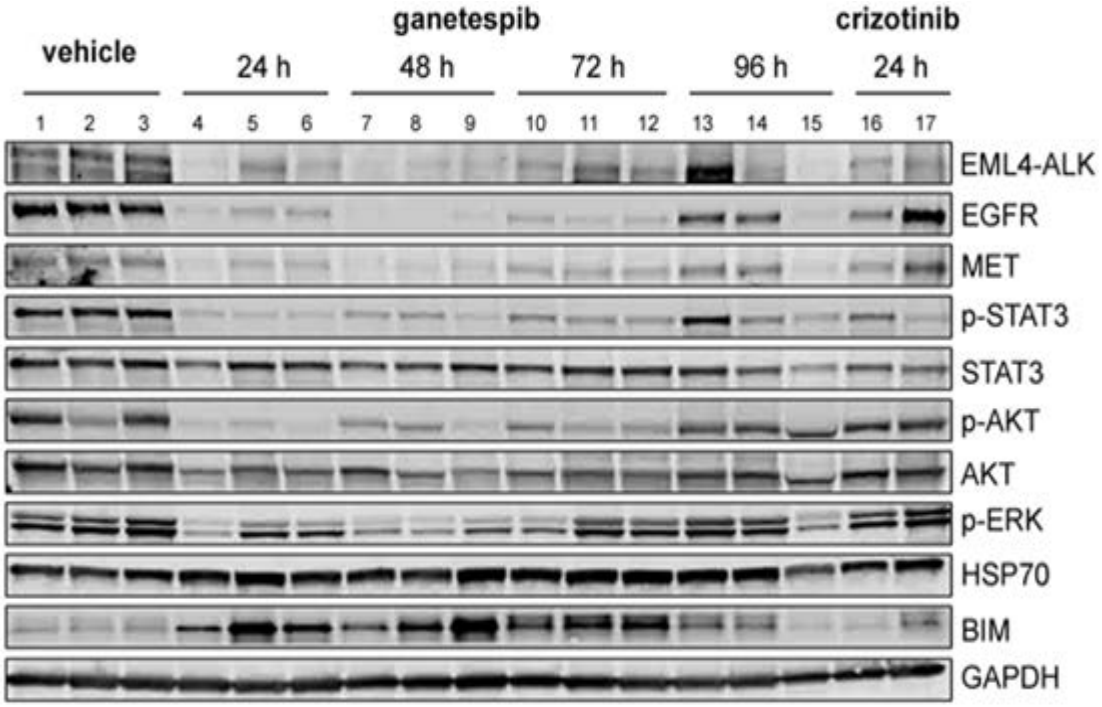

Figure 1: In Vivo Effects of Ganetespib on Expression of Hsp90 Client Proteins in H3122 Human NSCLC Xenograft Model SCID mice bearing H3122 tumors were treated with vehicle or a single bolus injection of ganetespib (50 mg/kg) at the indicated time points between 24 and 96 hours. Mice were also treated with a single bolus injection of crizotinib (50 mg/kg) for 24 hours. Tumors were resected and the levels of the indicated proteins determined by immunoblotting.

Ganetespib was also shown to reduce the expression of HIF1α levels in NSCLC tumor xenografts, as far as 150 μM from the nearest blood vessel, suggesting ganetespib can penetrate deep into the hypoxic regions of tumor tissue [data not shown]. In addition, exposure to a single bolus of ganetespib also resulted in reduction of CD31 expression (endothelial cell marker) by 39%, coordinate with a reduction in cell proliferation and rise of apoptosis and hypoxia (Figure 2).

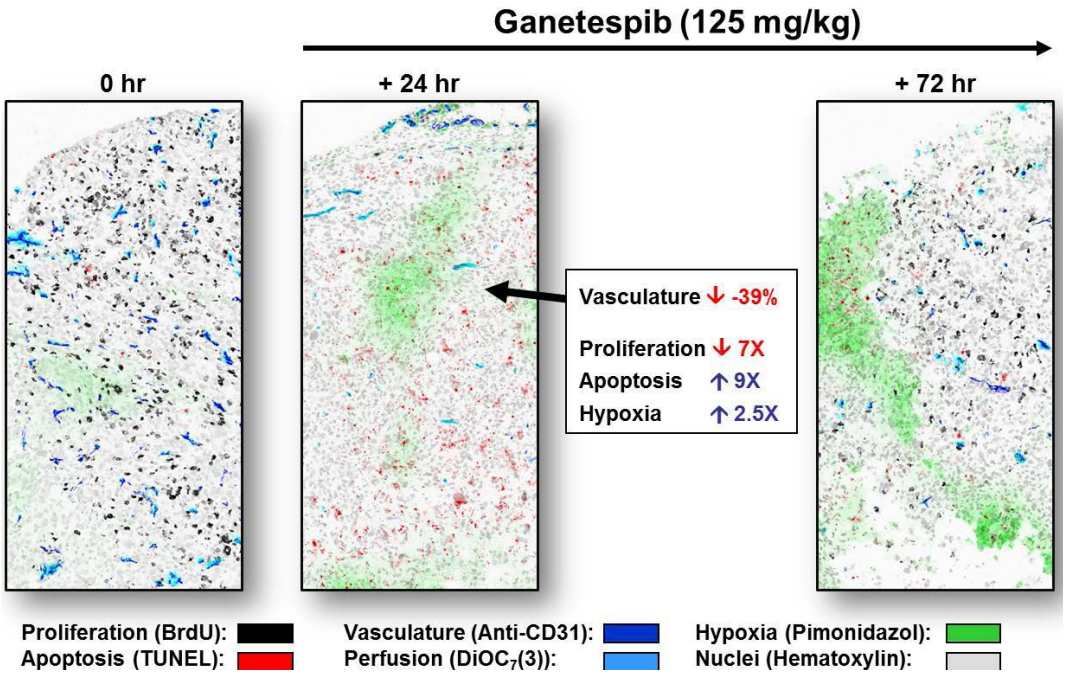

Figure 2: In Vivo Effect of Ganetespib on Tumor Vasculature, Proliferation, and Apoptosis in the NCI H1975 Xenograft Model. Mice were injected sc with 5 million NCI-H1975 tumor cells in 50% Matrigel. On D11, animals were treated with vehicle or a single bolus injection of ganetespib (125 mg/kg). Tumors were excised 24 hours after dosing and subject to quantitative image analysis for markers of proliferation (BrdU), apoptosis (TUNEL), vasculature (CD31), hypoxia (pimonidazole), and perfusion (DiOC7).

H3122 NSCLC tumor xenografts, with constitutively active ELM4-ALK fusion kinase, were also treated with ganetespib once weekly, with evidence of durable tumor regression, when compared with crizotinib (Figure 3).

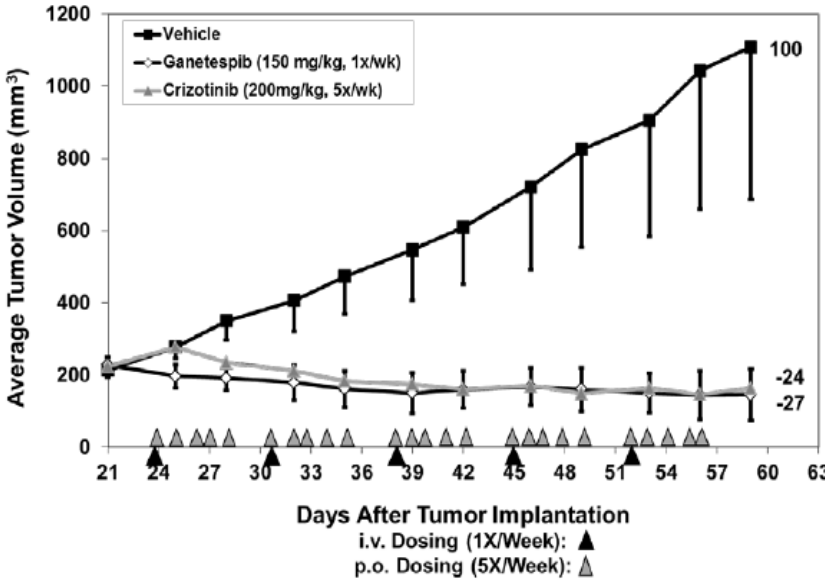

Figure 3: Anti-Tumor Activity of Ganetespib in the NCI H3122 Human NSCLC Xenograft Model . Mice (7/group) were injected sc with $5x10^6$ NCI H3122 tumor cells in 50% Matrigel. IV drug treatments (arrowheads) were performed starting on D24 and continued once/week for 5 weeks for ganetespib (150 mg/kg) and 5 times/week for crizotinib (200 mg/kg). %Tumor/Control values for D59 are indicated on the right. No excessive body weight loss (>20%) was observed in any animal. Error bars represent SEM.

Non-Clinical Pharmacokinetics

The pharmacokinetic (PK) profiles of ganetespib were evaluated in mice, rats, and monkeys following intravenous administration. Ganetespib displayed dose proportional PK in all species over the dose ranges tested. It is highly protein-bound and highly distributed throughout nearly all tissues, with limited distribution into the central nervous system. It is extensively metabolized in the liver to mainly glucuronide conjugates. The major route of excretion is in the feces. Ganetespib was highly cleared in mice and rats, and moderately cleared in monkeys. Mean terminal half-life ($T_{1/2}$) values for ganetespib in the multiple dose studies were approximately 6 and 11 hours in rats and monkeys, respectively. Ganetespib does not appear to accumulate after multiple dosing. No marked sex differences were observed in the PK of ganetespib in either rats or monkeys.

Preclinical Safety Pharmacology Studies and Toxicology Studies

Ganetespib was evaluated for safety pharmacology effects in a panel of receptor-binding assays in vitro and in a rabbit Langendorff heart preparation ex vivo. Rabbit hearts were perfused with vehicle (dimethylsulfoxide [DMSO] in Krebs solution) followed by escalating concentrations of ganetespib (10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4} M) for 15 minutes each. Ganetespib minimally decreased the rate of atrioventricular (AV) conductance at 10^{-6} and 10^{-5} M. At 10^{-4} M, the PQ interval was not measurable because of arrhythmia. Also at 10^{-4} M, the QRS duration increased, a second degree AV block was produced, and occasional supraventricular premature depolarization occurred. Other cardiac parameters were not significantly altered by ganetespib. The C_{max} at 1 mg/kg in cynomolgus monkeys correlates to a concentration of 10^{-8} M, when corrected for plasma protein binding, and is 100-fold lower than the minimum concentration of 10^{-6} M at which PQ interval increase was observed. At this concentration, there were no ganetespib-related changes in the mean arterial blood pressures or heart rates and no qualitative or quantitative ganetespib-related electrocardiogram changes.

To evaluate ocular toxicities, adult male Sprague Dawley rats received bolus IV injection of vehicle or 20 mg/kg/day ganetespib for 2 days. Twenty-four hours after the last dose, ocular toxicity was assessed by TUNEL staining of retinal tissues to detect apoptotic cell death. In subsets of animals, plasma and retinal tissues were collected to determine drug exposure. Ganetespib, at an exposure (AUCt 36.1 μM*h) that exceeded the 216-mg/m^3 human exposure (AUCt 22.5 μM*h), did not elicit retinal photoreceptor injury with no increase in TUNEL-positive cells.

In 3-month studies, ganetespib was administered on Days 1 and 15 of four 21-day cycles. Rats tolerated a dose of 20 mg/kg/dose, the NOAEL. Transient decreases in weight gain occurred at 50 and 100 mg/kg/dose, and early deaths occurred at 100 mg/kg/dose. Cynomolgus monkeys on the same regimen tolerated doses up to 7 mg/kg/dose, the NOAEL.

Clinical Pharmacokinetic Studies

Pharmacokinetic profiles in a Phase 1 study in solid tumors demonstrated that the concentration of ganetespib declined to approximately 10% of C_{max} within one hour of infusion termination and 1% of C_{max} within 8 to 10 hours. The mean time to reach C_{max} was 0.79 hours. There was no apparent drug accumulation with once weekly dosing. The mean ± SD terminal $T_{1/2}$ was approximately 7.54 ± 2.64 h and plasma drug clearance was 52.59 ± 17.80 L/h (28.55 + 9.33 L/h/m^2). Clearance and volume of distribution were approximately constant across doses. AUC increased in proportion to dose (Figure 4) [34]:

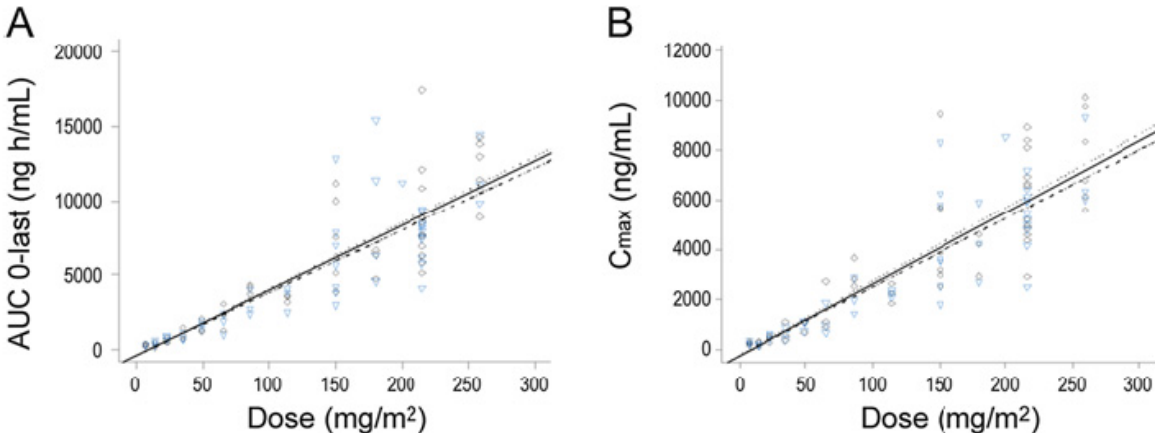

Figure 4. Pharmacokinetic linearity plots. (A) AUC vs. Dose and (B) Cmax vs. Dose. Solid line represents linear regression of D1 (diamond) and D15 (triangle) data combined. For D1 and 15 combined, coefficients of determination for AUC and Cmax were 0.75 and 0.76, respectively [34].

Clinical Experience

Ganetespib has been studied in 5 completed Synta-sponsored clinical trials and 3 completed Synta-sponsored studies in normal healthy volunteers. Ganetespib is currently being studied in 6 ongoing Synta-sponsored clinical trials and 17 investigator-sponsored clinical trials. In Phase 1 studies, ganetespib was well tolerated as a weekly infusion for 3 weeks of a 4 week cycle, with the maximum tolerated dose at 216 mg/m^2 and recommended Phase 2 dose at 200 mg/m^2. A recent Phase 2 study of ganetespib monotherapy in previously treated patients with non-small cell lung cancer (NSCLC) demonstrated 4 objective responses of 99 enrolled patients, stratified by mutant EGFR, mutant KRAS, or neither mutation [22]. These 4 patients were found to harbor anaplastic lymphoma kinase (ALK) gene rearrangement on retrospective analysis. PFS rates at 16 weeks were 13.3% for the mutant EGFR cohort, 5.9% for the mutant KRAS cohort, and overall 19.7% for the remaining cohort which included the 4 patients who achieved a partial response [22]. Ganetespib has also been tested in combination with docetaxel (Synta-sponsored Study 9090-07) and was found to be tolerable at a dose of 150 mg/m^2 on day 1 and 15, with docetaxel at 75 mg/m^2 on day 1.

Potential Drug Interactions

Inhibition and induction potentials of ganetespib were investigated in human liver microsomes and human hepatocytes. Ganetespib is a substrate for P-gp but not BRCP. Ganetespib is an inhibitor of CYP2C19 and CYP3A4 (midazolam specific), but is not an inducer of CYP or UGT enzymes. In liver microsomal studies, inhibition of CYP1A2, CYP2B6, CYP2D6 and CYP3A4 (testosterone-specific) by ganetespib was less than 50% at concentrations up to 10 μM (IC50 > 10 μM, maximum solubility conditions); ganetespib inhibited activities of CYP2C8, CYP2C9, CYP2C19 and CYP3A4 (midazolam-specific) with IC50 values of 9.8, 8.3, 1.0, and 1.1 μM, respectively. Inhibition of CYP2C8, CYP2C9, and CYP2C19 were competitive with inhibition constant (Ki) values of 3.2, 4.1, and 0.28 μM, respectively, whereas inhibition of CYP3A4 (midazolam specific) was non-competitive with a Ki value of 1.8 μM. Inhibition of CYP enzymes was reversible in all cases. In human hepatocytes, ganetespib did not induce CYP1A2, CYP2B6, or CYP3A4 at concentrations up to 10 μM. No increases in the levels of CYP1A2, CYP2B6, CYP3A4, UGTA1, and UGT1A6 were observed by Western Blot analyses after incubation of ganetespib in human hepatocytes.

A panel of potential co-medications (atorvastatin, dexamethasone, fentanyl, furosemide, morphine, and warfarin) was evaluated for potential drug interactions with ganetespib via hepatic metabolism using human cryopreserved hepatocytes suspensions. Ganetespib in vitro clearance was not affected by any of the co-medications tested at clinically relevant concentrations. Ganetespib did not markedly affect the CYP3A4-mediated metabolism of atorvastatin, dexamethasone, fentanyl, or warfarin. Ganetespib at 20 μM inhibited UGT mediated metabolism of potential co-medications, morphine (mainly UGT2B7), and furosemide (UGT1As), by approximately 30% in human hepatocytes at clinically relevant concentrations of these medications.

Due to evidence of increase in QTc interval 24 hours after the dose of ganetespib in a pharmacology study of healthy volunteers (Investigator's Brochure), certain drugs known to be associated with QTc prolongation (Appendix C) should not be used by patients treated with ganetespib. The use of any medication that has the potential for QTc prolongation and has been linked to the occurrence of torsades de pointes is strictly prohibited. Ondansetron has been associated with QTc prolongation and the occurrence of torsades de pointes. Therefore it should not be used in patients being treated with ganetespib. The use of all other serotonin 5HT3 antagonists is acceptable (e.g., palonosetron, granisetron, or tropisetron).

2.3 Ziv-aflibercept

Mechanism of Action

Angiogenesis is one of the hallmarks of carcinogenesis and malignant tumors are dependent upon angiogenesis for oxygen support, growth, and metastasis. VEGF, the key growth factor in angiogenesis, is comprised of 5 isoforms (VEGF-A, -B, -C, -D, -E, and placental growth factor [PlGF]). These growth factors exert their action through 3 tyrosine kinase receptors, VEGFR1, VEGFR2 and VEGF receptor 3 (VEGFR3). Ziv-aflibercept is a recombinant fusion protein consisting of human vascular endothelial growth factor

(VEGF) receptor extracellular domains fused to the Fc portion of human immunoglobulin G1 (IgG1). Ziv-aflibercept contains portions of the extracellular domains of 2 different vascular endothelial growth factor receptors (VEGFRs): VEGFR1 (also known as Flt-1) and VEGFR2 (also known as KDR or Flk-1). It acts as a high-affinity soluble VEGFR decoy receptor, and has high affinity for VEGF-A, VEGF-B, and PIGF. The affinity constants (KD) for binding to 2 human isoforms of VEGF, VEGF165 and VEGF121, are 0.50 pmol/L and 0.36 pmol/L, respectively. The KD for human PlGF2 is 39 pmol/L. The binding of ziv-aflibercept to its ligands in vivo is expected to block tumor angiogenesis and vascular permeability.

Nonclinical Toxicology Studies

General toxicity studies were conducted in cynomolgus monkeys and based on weekly and every two week intravenous administration of ziv-aflibercept for up to 6 months, and consistent with inhibition of the VEGF pathway previously reported with other anti-VEGF agents. Target organs indentified in these studies included bone (interference with growth plate maturation of long bones and osteocartilaginous exostoses of vertebrae), kidney (frequently increased glomerular mesangial matrix, occasionally hyperplasia of parietal epithelium, and periglomerular fibrosis), adrenals (decreased vacuolation with inflammation), nasal cavity (atrophy/loss of the septum and/or turbinates), kidney (glomerulopathy with inflammation), ovary (decreased number of maturing follicles, granulosa cells, and/or theca cells). Other microscopic findings in the 6-month chronic toxicity study included vascular alterations in the choroid plexus and digestive tract, vascular degeneration and fibrosis in several tissues including the heart, and hepatic portal inflammation and periportal necrosis.

Ziv-aflibercept was shown to alter fertility parameters in sexually mature male and female monkeys treated for 6 months. These effects were noted at plasma exposures of free ziv-aflibercept that were close to exposures in patients at the recommended pharmacological doses and were considered to impact fertility in both males and females. Inhibition of the female reproductive function by anti-VEGF drugs is related to the key role of VEGF-mediated angiogenesis in follicular and luteal development. The effects of ziv-aflibercept on sexually mature male and female fertility were reversible.

The safety pharmacology studies showed that ziv-aflibercept reduced vascular density in certain normal tissues in mice, increased blood pressure in rats and mice and delayed wound repair and healing in rabbits. Detectable effects these parameters were noted at doses that were lower than the optimal pharmacologic doses determined in tumor bearing mice. Maximal effects on wound healing and blood pressure were noted only at doses in the same range as pharmacologically active doses. The increase in blood pressure reported in rodents was reversible and was reported in patients treated with ziv-aflibercept. The reversibility of the effect on wound repair and healing was not evaluated. In full-thickness excisional and incisional skin wound models, ziv-aflibercept administration reduced fibrous response, neovascularization, epidermal hyperplasia/re-epithelialization, and tensile

strength. Ziv-aflibercept had no effects on respiratory function in rats or on thrombus formation in rabbits.

Pharmacokinetic Studies

Plasma concentration of free and VEGF-bound ziv-aflibercept were measured using specific enzyme-linked immunosorbent assays (ELISA). Free ziv-aflibercept concentrations exhibited linear pharmacokinetics in the dose range of 2-9 mg/kg. Following 4 mg/kg every two week administration schedule, the elimination half-life of free ziv-aflibercept was approximately 6 days (range 4-7 days). Steady state concentrations of free ziv-aflibercept were reached by the second dose. The accumulation ratio for free ziv-aflibercept was approximately 1.2 after an administration of 4 mg/kg every 2 weeks. Based on population pharmacokinetic analyses in patients with mild and moderate hepatic impairment, there was no effect of total bilirubin, aspartate aminotransferase, and alanine aminotransferase on the clearance of free ziv-aflibercept. There are currently no data available for patients with severe hepatic impairment (defined as total bilirubin >3 times upper limit of normal and any SGOT/AST). Based on population pharmacokinetic analyses of patients with mild, moderate, and severe renal impairment, there was no clinically observed effect of creatinine clearance on the clearance of free ziv-aflibercept**.**

Summary of Clinical Studies
To date, the clinical development of ziv-aflibercept encompasses a total of 41 clinical oncology trials (25 Sanofi trials and 16 NCI trials) in more than 3700 cancer patients mostly with advanced solid malignancies as well as 2 clinical trials in 76 healthy subjects (PDY6655 and PDY6656). Doses have been administered up to 800 μg/kg SC twice weekly, 7 mg/kg IV every 2 weeks (q2w), and 9 mg/kg IV every 3 weeks (q3w).

Based on combination Phase I dose-escalation studies conducted to evaluate safety, PK, and antitumor activity in patients with solid malignancies, the recommended Phase II dose (RP2D) of ziv-aflibercept was established at 4 mg/kg administered intravenously every 2 weeks when combined with chemotherapy.

In Phase III combination studies, ziv-aflibercept at a dose of 4 mg/kg administered intravenously every 2 weeks was combined with standard doses of the following cytotoxic agents: oxaliplatin/5-fluorouracil/leucovorin (FOLFOX4), [TCD6117]), irinotecan/leucovorin/5-fluorouracil (irinotecan/LV5FU2, [TCD6118]), and gemcitabine or gemcitabine and erlotinib (TCD6121), gemcitabine (EFC10547/VANILLA), and irinotecan/5-FU/leucovorin (FOLFIRI, [EFC10262/VELOUR]). Additional Phase III studies have also combined ziv-aflibercept at a dose of 6 mg/kg every 3 weeks in combination with standard doses of docetaxel (Taxotere®)/cisplatin/5-fluorouracil (TCF, [TCD6119]), docetaxel or docetaxel/cisplatin or pemetrexed (TCD6120), and docetaxel (EFC10261/VITAL).

FDA Approval was obtained based on results of Study EFC10262/VELOUR, a multinational, randomized, double-blind study, comparing the efficacy of ziv-aflibercept

administered at a dose of 4 mg/kg intravenously every 2 weeks versus placebo in patients with metastatic colorectal cancer treated with irinotecan /5-FU combination (FOLFIRI) after failure of an oxaliplatin based regimen. The efficacy conclusion from EFC10262/VELOUR was that ziv-aflibercept administered at a dose of 4 mg/kg over 1 hour, every 2 weeks, in combination with the FOLFIRI regimen demonstrated a statistically and clinically significant improvement in overall survival (OS), progression free survival (PFS) duration and a significantly higher overall response rate (ORR) compared to placebo/FOLFIRI. The addition of ziv-aflibercept to FOLFIRI gave no new toxicity signals but did enhance some toxicities of FOLFIRI, namely diarrhea, asthenia, decrease appetite, weight decrease, palmar plantar erythrodysesthesia syndrome, and hematological abnormalities (with the exception of anemia). Grade 3 or 4 events occurred with >2% higher incidence in the ziv-aflibercept/FOLFIRI arm compared to placebo/FOLFIRI arm, and included neutropenia, hypertension, diarrhea, asthenia, leucopenia, stomatitis and ulceration, infection, neutropenic complications and gastrointestinal (GI) and abdominal pain.

The risk of treatment-emergent adverse events identified as possible anti-VEGF class specific adverse events were significantly increased and these were more frequently all grade hypertension and hemorrhage. Analyses of pre-specified subgroups during EFC10262/VELOUR, showed no statistically significant differences across subgroups (gender, race, age, of body weight, creatinine clearance, ECOG PS at baseline) with regard to incidences of hypertension, hemorrhage, venous thromboembolic events, arterial thromboembolic events, wound healing complications, renal failure events, acute drug reactions. The safety profile (either VEGF-blockade adverse events or chemotherapy induced toxicities) in patients with renal or liver function impairment did not significantly differ when compared to that observed in patients with normal renal or liver function at baseline. The safety profile of ziv-aflibercept in combination with FOLFIRI was also comparable between patients with or without prior bevacizumab.

Since this current study (14-C-0150) opened, there have been two dose limiting toxicities in patients on DL1. The first patient, who had a history of peptic ulcer disease, had grade 3 recurrent epigastric pain despite optimal management. The second patient had abdominal pain with colon cancer; a CT scan showed progressive disease and bowel perforation. This patient died on cycle 1 day 22. Because bowel perforation has been seen with ziv-aflibercept, it may have contributed to the toxicity. In response to these events the protocol was amended to add lower dose levels.

2.4 ^{89}Zr-labeled, EGFR-targeting Antibody Panitumumab PET/CT

Panitumumab is a fully human monoclonal antibody (mAb) that targets EGFR and is approved for use by the FDA for the treatment of EGFR-expressing metastatic colorectal cancer with disease progression [35]. Panitumumab competes with endogenous ligands such as epidermal growth factor and tumor growth factor α (TGF-α) to block stimulation of the EGF receptor.

^{89}Zr has emerged as a promising positron-emitting radionuclide [36-39] for diagnostic immune-PET imaging. The half-life (78.4 h) provides a good match with the biological half-life of an intact mAb. Based on findings from recent clinical trials in Europe, ^{89}Zr-labeled mAbs are safe for human use [39]. It is also being used for imaging in NCI Protocol # 06-C-0164 with no adverse events. We anticipate that ^{89}Zr-immuno-PET with panitumumab as targeting ligand will prove to be an ideal imaging modality to quantify EGFR expression as a biomarker to guide patient selection, therapy, and dosing in the future. No clinical decisions will be made based on the ^{89}Zr-panitumumab imaging findings in this study. Use of ^{89}Zr-panitumumab as an investigational agent is covered by a cross-reference letter from IND 116,229, held by DCTD/CIP.

^{89}Zr-panitumumab has been prepared with high radiochemical purity and specific activity at the Frederick National Laboratory for Cancer Research. The immunoconjugate was found to be stable with respect to loss of the radio-isotope in human serum. Immuno-PET experiments indicated that ^{89}Zr-panitumumab shows excellent potential as a PET tracer for specific noninvasive delineation of EGFR-positive tumors in vivo.

Human cell lines with low, medium, and high levels of EGFR (BT-474, MDA-MB-231, and MDA-MB-468, respectively) were implanted subcutaneously as xenografts in athymic nude mice (Figure 5)[40]. ^{89}Zr-panitumumab was administered intravenously, and a CT scan followed by a static PET scan was performed at 96 hours. EGFR protein expression correlated well with the PET tracer present in tumors.

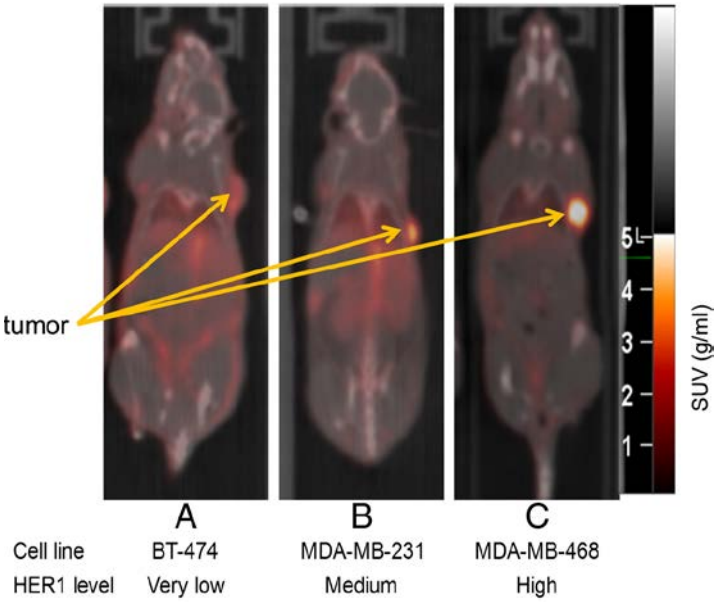

Figure 5. Tumor uptake of ^{89}Zr-panitumumab in sc xenograft models with different levels of EGFR expression. 10.18 ±1.24 MBq of ^{89}Zr-panitumumab were administered IV via tail-vein, and a 5 min CT scan followed by a 30min static PET scan were performed 96-h post-injection [40].

Biodistribution studies of ^{89}Zr-panitumumab were performed in male and female mouse cohorts, which were injected with ~100 μCi of agent via tail vein injection. A fraction of the animals were sacrificed daily up until 6-days post injection. The organs, blood, and carcass activity was measured and recorded as %ID/g. For the hollow organs (i.e., gut,

urinary bladder) the total activity within the organ was recorded. Minimal radiotracer was excreted from the body over the entire 6-day period; the loss via urinary excretion was likewise minimal. Human dose estimates were made using appropriate correction factors (to account for the differences in percent total body weight of each solid organ) to calculate residence times for each organ. OLINDA/EXM 1.1 software was used to calculate human dose estimates (Table below). Based on these figures, we intend to administer a dose of not more than 1.0 mCi (mass dose <1 mg) to patients in this protocol.

^{89}Zr-labeled, EGFR-targeting antibody panitumumab human dosimetry estimates for the organs receiving the highest dose:

Target Organ	**^{89}Zr-panitumumab male/female (rads/mCi)**
Heart	10.1/12.7
Lungs	3.14/3.77
Liver	2.74/3.47
Red marrow	2.57/3.15
Spleen	2.61/2.87
Effective Dose (rem/mCi)	1.92/2.47

We have early human experience with ^{89}Zr-panitumumab imaging in the ongoing Phase II Study of BAY 43-9006 (Sorafenib) in Combination with Cetuximab (Erbitux™) in EGFR Expressing Metastatic Colorectal Cancer (CRC) Protocol 06-C-0164. So far, two patients have undergone imaging with good tolerability and no adverse side effects.

3 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed recurrent or metastatic gastrointestinal carcinomas, non-squamous non-small cell lung carcinomas, urothelial carcinomas, and sarcomas with disease progression after at least one line of standard therapy. Disease should have progressed following all treatments known to prolong survival, unless a given treatment is contraindicated.

- Patients with colorectal carcinoma must have progressed through at least two lines of standard chemotherapy in the metastatic setting.
- Patients with non-small cell lung cancer with known sensitizing EGFR mutation and/or ALK rearrangement should have received prior erlotinib and/or crizotinib, respectively.
- Patients with urothelial carcinoma will have progressed on prior platinum-based therapy or for which platinum-based therapy is contraindicated.
- Patients enrolled on the expansion phase of the protocol must demonstrate EGFR expression by immunohistochemistry on archival tumor samples prior to undergoing ^{89}Zr-panitumumab PET/CT scans.

3.1.2 Age ≥18 years of age.

3.1.3 ECOG performance status < 2 (see Appendix A).

3.1.4 Life expectancy > 3 months.

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

– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	≤1.5 X institutional upper limit of normal
– AST(SGOT)/ALT(SGPT)	≤3 X institutional upper limit of normal
– creatinine	≤1.2X institutional upper limit of normal
	OR
– creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal
– urine protein/creatinine	< 1 mg/mg
– INR	< 1.5

3.1.6 Cardiac function within institutional normal limits on echocardiogram.

3.1.7 Patients must have blood pressure no greater than 140 mmHg (systolic blood pressure) and 90 mmHg (diastolic blood pressure) for eligibility. Initiation or adjustment of antihypertensive medications is permitted prior to study entry provided that the average of three blood pressure measurements at enrollment visit is less than 140/90 mmHg.

3.1.8 The effects of ganetespib on the developing human fetus are unknown. For this reason and because anti-angiogenic agents similar to ziv-aflibercept are known to be teratogenic, women of child-bearing potential and men must agree to use two forms of contraception (hormonal or barrier method of birth control; abstinence; sterilization) prior to study entry, for the duration of study participation, and for 3 months after completing study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use two forms of contraception prior to the study, for the duration of study participation, and for 3 months after completion of administration of both ganetespib and ziv-aflibercept.

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

3.1.10 During the escalation phase of the protocol, patients may have evaluable or measurable disease. During the expansion phase of the protocol, patients must have 1) measurable disease, 2) disease amenable to biopsy and 3) willingness to undergo pre- and post-treatment biopsies.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 3 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 3 weeks earlier.

3.2.2 Patients who are receiving any other investigational agents.

3.2.3 Patients with known active brain metastases or carcinomatous meningitis are excluded from this clinical trial. Patients whose brain metastatic disease status has remained stable for ≥ 4 weeks following treatment of brain metastases are eligible to participate at the discretion of the principal investigator.

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

3.2.5 Patients with known serious cardiac illness or medical conditions, including but not limited to:

- Clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, unstable angina or history of myocardial infarct within 6 months prior to enrollment, or indwelling temporary pacemaker
- Ventricular tachycardia or a supraventricular tachycardia that requires treatment with antiarrhythmic agents
- Second- or third-degree atrioventricular block unless treated with a permanent pacemaker
- Complete left bundle branch block
- History of long QT syndrome or a family member with this condition

3.2.6 No major surgery within 4 weeks prior to enrollment or history of gastrointestinal bleeding within 3 months prior to enrollment. No signs or symptoms of active bleeding or nonhealing ulcer will be permitted at study entry. Patients with central pulmonary tumors with evidence of bronchial invasion, or presenting with hemoptysis will be excluded.

3.2.7 QTc > 470 msec on electrocardiogram (by Bazett's; average of triplicate recordings at the discretion of the PI) will exclude patients from entry on study. Medications that are known to cause QTc interval prolongation are prohibited for patients entering on trial. Patients for whom a given medication that may cause QTc interval prolongation cannot be discontinued, may be eligible at the discretion of the study PI, provided QTc interval criteria is met at enrollment. A comprehensive list of agents with the potential to cause QTc prolongation can be found in Appendix C and at http://crediblemeds.org.

3.2.8 Pregnant women and women who are breastfeeding are excluded from this study because the effects of the study drugs on the developing fetus are unknown.

3.2.9 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with ganetespib and ziv-aflibercept. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.2.10 *Substrates of CYP3A4 or CYP2C19*

Preliminary results of a clinical drug-drug interaction study, examining the effect of ganetespib on the pharmacokinetics of the CYP2C19-sensitive probe omeprazole, show a modest (20%) increase in omeprazole exposure when coadministered with ganetespib. In vitro data implies expectation of greater interaction with CYP2C19 substrates than with CYP3A4 substrates. Caution is advised when sensitive narrow therapeutic range CYP3A4 or CYP2C19 substrates are concomitantly administered.

Inhibitors of P-Glycoprotein Efflux Transporters

Concomitant medications that are strong inhibitors of P-glycoprotein efflux transporters should be used with caution during the study; examples of these medications include ritonavir, cyclosporine, verapamil, erythromycin, ketoconazole, itraconazole, quinidine, and elacridar.

3.2.11 Concurrent anticoagulation will be permitted providing the patient is receiving a stable dose of anticoagulants before study entry. Patients receiving anticoagulants will be eligible for this trial. Evidence of clinically significant bleeding diathesis or underlying coagulopathy (e.g., INR > 1.5 without vitamin K antagonist therapy) will not be permitted

3.3 Inclusion of Women and Minorities

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

3.4 Screening Evaluation

3.4.1 Histologic confirmation of primary tumor tissue or of known recurrence will be required from each participant to confirm diagnosis. Additionally, EGFR expression by immunohistochemistry on archival tissue will be required for patients undergoing ^{89}Zr-panitumumab scans.

3.4.2 History and physical examination: Complete history and physical examination (including height, weight, vital signs, and performance score) will be conducted within 72 hours prior to enrollment.

3.4.3 Imaging Studies (Baseline): Every participant should have an evaluation of known sites of disease as part of the baseline evaluation. All patients will be required to undergo a CT scan of the chest/abdomen/pelvis to evaluate sites of disease within 28 days prior to enrollment. MRI evaluation of site of disease may be performed in lieu of CT evaluation at the discretion of the principal investigator if it is the opinion of the investigator that this modality would provide a more accurate assessment of disease than a CT would, for a given site.

3.4.4 Electrocardiogram within 1 week prior to enrollment. Echocardiogram evaluation to assess cardiac function must be performed within 4 weeks of enrollment.

3.4.5 Laboratory Evaluation: Baseline laboratory data are to be obtained within 72 hours prior to enrollment:

- Hematological Profile: CBC with differential.
- Biochemical Profile: albumin, total bilirubin, BUN, calcium, creatinine, SGOT [AST], SGPT [ALT], amylase, lipase, magnesium, potassium, and sodium.
- Coagulation Profile: PT, PTT, INR.
- Serum pregnancy test for female participants of childbearing potential.

3.4.6. All study participants must have a baseline eye exam by a qualified ophthalmologist within 4 weeks prior to enrollment and as clinically indicated thereafter.

4 REGISTRATION PROCEDURES

4.1 Registration Process

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the Web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) (ncicentralregistration-l@mail.nih.gov). After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

Off-Study Procedure: Authorized staff must notify the Central Registration Office (CRO) when a patient is taken off-study. An off-study form from the Web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) (ncicentralregistration-l@mail.nih.gov).

5 TREATMENT PLAN

This is an open-label Phase I trial evaluating the combination of ganetespib, Hsp90 inhibitor, and ziv-aflibercept, VEGF-trap, in patients with refractory gastrointestinal carcinomas, non-squamous non-small cell lung carcinomas, urothelial carcinomas, and sarcomas, whose disease has progressed following at least one line of standard therapy.

Reported adverse events and potential risks for ganetespib and ziv-aflibercept are described in Section 7. Appropriate dose modifications for ganetespib and ziv-aflibercept are described in Section 6.

History and physical examination can be done up to 3 days before the start of a new cycle. Patients will be examined at the Clinical Center on days 1, 8, and 15 of each cycle, prior to treatment. Each cycle is 28 days (± 1 day due to scheduling conflicts).

Labs (CBC with differential; serum chemistries) will be performed on days 1, 8, and 15 of each cycle (+/- 1 day during the cycle and up to 3 days before start of a new cycle).

Electrocardiogram will be done before each ganetespib administration and approximately 24 hours after drug administration during each week of treatment of the first cycle. For subsequent cycles, electrocardiogram will be done before each ganetespib administration with post-treatment electrocardiogram as clinically indicated.

All study participants must have a baseline eye exam by a qualified ophthalmologist within 4 weeks prior to enrollment and as clinically indicated thereafter.

CT scans will be performed at baseline, and repeat-imaging scans will be performed every 2 cycles. MRI evaluation of site of disease may be performed in lieu of CT evaluation at the discretion of the principal investigator if it is the opinion of the investigator that this modality would provide a more accurate assessment of disease than a CT would for a given site.

The starting dose will start at dose level 1 per dosing schema below. Ganetespib will be dosed based on body surface area (mg/m^2). Ziv-aflibercept will be dosed based on body weight (mg/kg).

5.1 Agent Administration

5.1.1 Ganetespib Administration

Ganetespib will be administered intravenously, over one hour, weekly, on days 1, 8, and 15 of each 28-day cycle. During the expansion phase, for cycle 1 only, ganetespib will be administered intravenously on days 8 and 15 of the 28-day cycle, with omission of day 1 treatment in order to accommodate tumor biopsies (*see dosing schema below).

5.1.2 Ziv-aflibercept administration

Ziv-aflibercept will be administered intravenously, over one hour, every 2 weeks, on days 1 and 15 of each 28-day cycle.

Dosing Schema:

Dose Level	Ganetespib (IV) days 1, 8, and 15*	Ziv-aflibercept (IV) days 1 and 15
-2	80 mg/m^2	3 mg/kg
-1	100 mg/m^2	3 mg/kg
1	100 mg/m^2	4 mg/kg
2	150 mg/m^2	4 mg/kg

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

Due to evidence of increase in QTc interval 24 hours after the dose of ganetespib in a pharmacology study of healthy volunteers (Investigator's Brochure), certain drugs known to be associated with QTc prolongation (Appendix C) should not be used by patients treated with ganetespib. The use of any medication that has the potential for QTc prolongation and has been linked to the occurrence of torsades de pointes is strictly prohibited. **Ondansetron has been associated with QTc prolongation and the occurrence of torsades de pointes.** Therefore it should not be used in patients being treated with ganetespib. The use of all other serotonin 5HT3 antagonists is acceptable (e.g., palonosetron, granisetron, tropisetron).

5.2 Definition of Dose-Limiting Toxicity

Determination of dose-limiting toxicity will be based on toxicities observed in the first cycle of therapy. Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined below:

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.

1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

Dose limiting toxicity (DLT) is defined as an adverse event that is related (possibly, probably, or definitely) to administration of study drugs and fulfills one of the following criteria.

5.2.1 Grade ≥ 3 Non-Hematological Toxicity

Grade ≥ 3 non-hematological toxicity felt to be related to study medications will be considered dose-limiting with the following clarifications:

5.2.1.1 Diarrhea Grade 3 will only be considered dose-limiting if it is refractory to treatment as outlined in Section 5.3.2, Supportive Care Guideline, and unable to be corrected to Grade 2 or less within 24 hours. Bloody or Grade 4 diarrhea will be dose-limiting.

5.2.1.2 Nausea and vomiting Grade 3 will only be considered dose-limiting if it is refractory to anti-emetic therapy and unable to be corrected to Grade 1 or less within 24 hours as outlined in Section 5.3.1.

5.2.1.3 Rise in creatinine to Grade 3, not corrected to Grade 1 or less within 48 hours with IV fluids will be considered dose-limiting. All Grade 4 rises in creatinine will be dose limiting.

5.2.1.4 Grade ≥ 3 metabolic toxicities unable to be corrected to Grade 1 or baseline within 48 hours (hypocalcemia or hypercalcemia, hypomagnesemia or hypermagnesemia, and hyponatremia) will be considered dose limiting. For hypokalemia or hyperkalemia, grade ≥ 2 toxicities unable to be corrected to grade 1 or less within 48 hours will be considered dose limiting. Grade 4 metabolic toxicities that are symptomatic will be considered dose limiting regardless of duration or ability to correct.

5.2.1.5 Any Grade 4 QTc prolongation will be considered dose limiting and will require treatment discontinuation

5.2.2 Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with bleeding.

5.2.3 Grade 4 neutropenia ≥ 5 days or febrile neutropenia.

5.2.4 Any degree or anemia, leukopenia in the absence of grade 4 neutropenia ≥ 5 days, or lymphopenia will not be considered dose limiting.

5.2.5 Any degree of alopecia will not be considered dose limiting.

5.2.6 Grade 3 fatigue of greater than 1 week duration.

5.2.7 Failure to tolerate 100% of the dosing in the first cycle.

5.3 General Concomitant Medication and Supportive Care Guidelines

The predominant toxicity observed in clinical and non-clinical toxicology studies was diarrhea, nausea, vomiting, and abdominal pain. Anemia was more commonly seen with ziv-aflibercept. Weekly blood counts and chemistry panels will be obtained prior to treatment each week. If any weekly evaluation demonstrates grade ≥ 2 neutropenia or thrombocytopenia, treatment will proceed but a repeat hematology assessment will be obtained prior to the next treatment or within a week if the last treatment received was on Day 15 of the cycle. Platelet count must improve to Grade 1 or better and neutrophil count must improve to Grade 2 or better prior to dosing.

All patients will be provided with the best available supportive care. All concurrent medications should be documented prior to initiation of treatment, and be periodically reviewed with the patient.

Based on in vitro and in vivo data, ganetespib is primarily metabolized (glucuronidated) by UGT1A9 and to a lesser extent by UGT1A1, UGT1A3, and various P450 enzymes. It is also a substrate for P-glycoprotein, but is primarily eliminated through glucuronidation. In in vitro studies, ganetespib is a moderate inhibitor of CYP2C19 and CYP3A4. No dedicated drug-drug interaction studies have been conducted for ziv-aflibercept. Due to the potential for drug-drug interactions with study agents, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, and alternative therapies. Concurrent use of strong P450 inducers or inhibitors will not be permitted. Concurrent use of moderate or strong UGT1A9 inhibitors (e.g., efavirenz and propofol) should be avoided. Concurrent use of inducers of UGTs (e.g., rifampin, phenobarbital, phenytoin, and St. John's Wort) may significantly increase ganetespib clearance, resulting in reduced plasma concentration and should be avoided. Concurrent use of weak P450 inducers, inhibitors, or substrates will be permitted at the discretion of the Principal Investigator.

The QTc study in healthy volunteers has reported a modest increase in QT interval 24 hours post ganetespib dose. To date, clinical experience with ganetespib does not support evidence of a clinical safety risk for QTc interval prolongation and Torsade de Pointes or other uncontrolled arrhythmias. However, until the effect of ganetespib on QT interval is completely characterized, patients should avoid concomitant drugs that may cause QTc prolongation, see Appendix C.

5.3.1 Nausea/Vomiting

Anti-emetics will not be administered routinely prior to either ganetespib or ziv-aflibercept (VEGF-Trap). However, if a patient develops nausea/vomiting, anti-emetics such as but not limited to prochlorperazine, metoclopramide, 5-HT3 antagonists (**except for ondansetron**), or aprepitant may be given. In addition, if a patient develops nausea and/or vomiting that is Grade 2 or greater, antiemetics may be instituted prophylactically at the discretion of the investigator with subsequent treatments. Nausea and vomiting will be considered refractory if it does not resolve to ≤ Grade 1 within 24 hours.

5.3.2 Diarrhea

Prophylactic anti-motility agents will be permitted with treatment as diarrhea is a known toxicity of both agents and the established recommended dose of ganetespib was established based on prophylactic administration of anti-motility agents. Prophylactic treatment will start 1-2 hours before ganetespib administration. If diarrhea develops despite prophylactic treatment with anti-motility agents and does not have an identifiable cause other than study drug administration, addition of anti-motility agents such as tincture of opium (deodorized 10%), Lomotil (diphenoxylate HCl 2.5 mg + atropine sulfate 0.025 mg/tablet) dosed according to package insert, or loperamide 4 mg po after the first unformed stool with 2 mg po with every 2 hours as long as unformed stools continue (4 mg every 4 hours while asleep) may be used. No more than 16 mg of loperamide should be taken during a 24-hour period). This regimen can be repeated for each diarrheal episode and will continue for 12 hours after the first formed stool. Diarrhea will be considered refractory if it does not resolve within 24 hours ≤ to Grade 2 with the above measures. If the patient develops blood or mucus in the stool, dehydration, or hemodynamic instability, or fever along with the diarrhea, anti-diarrheals will be discontinued and the patient will be treated with IV fluids and antibiotics as medically indicated.

5.3.3 Neutropenia

To reduce the risk of severe myelosuppression events, a complete blood count (CBC) should be performed prior to each weekly treatment. Febrile neutropenia is a life-threatening complication requiring hospitalization and urgent broad-spectrum antibiotics, as well as an aggressive search for the source and microbial cause of the episode. Growth factors to prevent neutropenia will not be administered prophylactically. If necessary, they may be administered according to accepted American Society of Clinical Oncology (ASCO) guidelines to allow re-treatment.

5.3.4 Anemia

Symptomatic anemia should be treated with red blood cell transfusion and is recommended if the hemoglobin falls below 8 g/dL. The initiation of erythropoietic therapy for the management of chemotherapy-induced anemia follows the American Society of Hematology/ASCO clinical practice guidelines (http://www.asco.org).

5.3.5 Thrombocytopenia

Thrombocytopenia will be treated conservatively. In the absence of bleeding, or a necessary invasive procedure, platelet transfusions should be given for a platelet count ≤10,000/mm^3. If invasive procedure(s) is (are) planned, or the patient develops bleeding, platelet transfusions should be administered in accordance with the standard of practice, usually maintaining a platelet count above 50,000/mm^3.

5.4 Duration of Therapy

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Significant toxicity occurs despite 2 dose reductions as described in Section 6
- Pregnancy
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.5 Duration of Follow Up

Patients will be followed for 30 days after the last dose is administered or until one of the following occurs: patient enrolls on another protocol, patient receives standard of care, or death, whichever comes first. The follow-up will consist of a phone call between Days 27-30 after the last dose to evaluate adverse events that were ongoing and any new events that might be deemed related to the therapy. Toxicities felt to be possibly, probably, or definitely related to the study drugs that have not resolved or stabilized by Day 30 post-treatment will be followed until stabilization or resolution via phone calls as clinically indicated.

5.6 Criteria for Removal from Study

Patients will be removed from study for one of the following reasons: completed 30-day follow up period or toxicities are unresolved but stabilized, patient enrolls on another protocol, or patient receives standard of care. The reason for study removal and the date the patient was removed must be documented in the medical record and communicated by fax to Central Registration per Section 4.

6 DOSING DELAYS/DOSE MODIFICATIONS

Toxicities should have resolved to ≤ Grade 2 prior to starting the next cycle. Treatment may be delayed for a maximum of 2 weeks beyond the actual cycle length of 28 days for toxicities that develop and do not resolve as defined above. Beyond two weeks, the patient may remain in the study at the discretion of the PI. Treatment may be delayed for a maximum of ± 1 day

during a cycle due to unavoidable scheduling conflicts. If treatment is held during a cycle, that week's treatment will be omitted for the cycle and treatment will proceed with the following week's treatment as scheduled (e.g., if Day 8 ganetespib treatment is held, the next treatment will be Day 15 treatment with both agents).

Dose Modification Schema:

Baseline Dosing Schema

Dose Level	Ganetespib (IV)	Ziv-aflibercept (IV)
-2	80 mg/m^2	3 mg/kg
-1	100 mg/m^2	3 mg/kg
1	100 mg/m^2	4 mg/kg
2	150 mg/m^2	4 mg/kg

DLT attributed to Ganetespib alone

Schema A

Dose Level	Ganetespib (IV)	Ziv-aflibercept (IV)
-1a	80 mg/m^2	3 mg/kg

DLT attributed to Ziv-Aflibercept alone

Schema C

Dose Level	Ganetespib (IV)	Ziv-aflibercept (IV)
-1c	100 mg/m^2	2 mg/kg

DLT attributed to both agents

Schema B

Dose Level	Ganetespib (IV)	Ziv-aflibercept (IV)
-1b	80 mg/m^2	2 mg/kg

6.1 Dose Modifications

Dose modifications are defined below:

6.1.1 Grade 2 Drug-related toxicity: No changes will be made to the dose of either ganetespib or ziv-aflibercept for Grade 2 toxicities. Therapy will not be interrupted for Grade 2 hematologic toxicities.

6.1.2 Grade 3-4 Drug-related non-hematologic toxicities attributed to both drugs: Doses of both ganetespib and ziv-aflibercept will be held until toxicities recover to ≤ Grade 2 or baseline prior to re-initiating treatment at the next lower dose level. Electrolyte abnormalities will not require dose reduction if resolution to Grade 2 or less is documented within 72 hours. Dose modifications (per dosing Schema B) for nausea, vomiting, and diarrhea will be made only if they are refractory to treatment (See Section 5.2).

6.1.3 Grade 3 Drug-related hematologic toxicities: Both ganetespib and ziv-aflibercept

will be held until hematologic toxicities, except anemia, lymphopenia, or leucopenia in the absence of Grade 3 or higher neutropenia, have resolved to ≤ Grade 2 prior to re-initiating treatment at the same dose level.

6.1.4 Grade 4 Drug-related Hematologic Toxicities: Both ganetespib and ziv-aflibercept (VEGF-Trap) will be held until hematologic toxicities, except anemia, lymphopenia, or leucopenia in the absence of Grade 4 neutropenia, have resolved to ≤ Grade 2 prior to re-initiating treatment at the next lower dose level (per dosing Schema B).

6.1.5 Diarrhea attributed to both ganetespib and ziv-aflibercept: As diarrhea is an expected toxicity for both agents, and as the recommended dose of ganetespib was established in the setting of prophylactic loperamide, prophylactic anti-motility agents will be given 1 to 2 hours before ganetespib administration, and will be repeated every 4 hours for the first 12 hours. If diarrhea occurs despite prophylactic administration of anti-motility agents, supportive care guidelines will follow Section 5.3.2.

6.1.6 Ocular toxicities attributed to ganetespib: Dose of ganetespib will be held until toxicities recover to < Grade 2 or baseline prior to re-initiating treatment at the next lower dose level per Schema A (above).

6.1.7 QTc interval prolongation ≥ 500 msec (by Bazett's formula) attributed to ganetespib: Dose of ganetespib will be held until QTc interval is <500 msec or baseline prior to re-initiating treatment at the next lower dose level per Schema A (above). Dose of ziv-aflibercept will not be modified.

6.1.8 Proteinuria attributed to ziv-aflibercept: For proteinuria ≥ 1 grams/24 hours, dose of ziv-aflibercept will be held until proteinuria is < 1 grams/24 hours prior to re-initiating treatment at the same dose level. Dose reduction will occur for proteinuria ≥ 3 grams/ 24 hours or for recurrent proteinuria of ≥ 1 grams/24 hours per Schema C (above). Ziv-aflibercept will be discontinued for proteinuria with gross hematuria. Dose of ganetespib will not be modified for proteinuria.

6.1.9 Hypertension toxicity attributed to ziv-aflibercept:

CTCAE V4.0 Grade	**Action to be taken:**
Grade 1 (SBP 120-139 mmHg or DBP 80-89 mmHg)	Consider increased BP monitoring; Start anti-hypertensive medication if persistent. *For patients without prior antihypertensive therapy*, at the time of the hypertensive episode the initiation of calcium-channel blockers should be considered as a first-intent treatment. A close monitoring of the BP should be initiated for further adjustment in treatment, as needed. *For patients already under anti-hypertensive therapy*, efforts should be done to optimize the existing therapy before adding other agents as required to control the BP.

CTCAE V4.0 Grade	Action to be taken:
Grade 2 asymptomatic (SBP 140-159 mmHg or DBP 90-99 mmHg)	Start or add an additional anti-hypertensive agent and continue ziv-aflibercept per recommendations below. Close monitoring of BP for further adjustment, as needed. No dose modification and no delay.
Grade 3 (SBP ≥ 160 mmHg or DBP ≥ 100 mmHg)	Hold ziv-aflibercept for a maximum of 2 weeks, until recovery to < Grade 2. • If BP is controlled within 2 weeks delay: -First episode: re-administer ziv-aflibercept at the same dose -Subsequent episode: re-administer ziv-aflibercept with dose reduction as per Schema C (above). • If BP is still uncontrolled despite appropriate anti-hypertensive treatment and after 2 weeks delay, ziv-aflibercept will be discontinued and patient will go off study.
Grade 4 (Hypertensive crisis or Malignant hypertension)	Discontinue ziv-aflibercept. Patient will go off study.

6.1.10 For any Grade 3-4 arterial thromboembolic event, Grade 3-4 hemorrhage, Grade 3-4 venous thromboembolic event, GI perforation, reversible posterior leukoencephalopathy syndrome attributed to ziv-aflibercept, ziv-aflibercept will be discontinued and the patient will go off study.

6.1.11 Infusional reaction attributed to either ganetespib or ziv-aflibercept: Ganetespib contains a surfactant (polysorbate 80) which has been associated with hypersensitivity reactions with other medications administered by infusion. Ziv-aflibercept has also been associated with an antibody-associated infusional reaction. Symptoms have included pruritis, flushing, shortness of breath, chest tightness, dizziness, headache, increased systolic blood pressure and heart rate.

Severity of Symptoms	
Mild transient reaction	Give diphenhydramine HCl 25 mg to 50 mg IV, continue treatment, close monitoring of vitals q 5 min. for 15 min. after onset of symptoms.
Mild to moderate persistent reaction	Stop treatment; give dexamethasone 10 mg IV and diphenhydramine HCl 25 mg to 50 mg IV; may resume treatment after recovery of symptoms; pre-medication indicated for subsequent drug administration: pre-medication indicated prior to re-initiation: dexamethasone 12 mg PO and diphenhydramine HCl 25 mg to 50 mg PO approximately 4 to 6 hours prior to re-challenge
Severe symptoms (e.g., hypotension requiring pressor therapy or IV fluids, angioedema, respiratory distress requiring bronchodilator therapy, or generalized urticaria)	Stop treatment; give dexamethasone 10 mg IV and diphenhydramine HCl 25 mg to 50 mg IV; add bronchodilators as needed; patients may not receive further treatment.

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Ganetespib (NSC 777169)

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

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.

Below is the CAEPR for ganetespib. *Frequency is provided based on 423 patients.*

Version 2.0, January 27, 2014[1]

Adverse Events with Possible Relationship to Ganetespib (CTCAE 4.0 Term) [n= 423]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
CARDIAC DISORDERS			
		Atrial fibrillation	
		Cardiac arrest	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
Diarrhea			***Diarrhea (Gr 2)***
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***

HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
		Sepsis	
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		
	Hypokalemia		
	Hyponatremia		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		
PSYCHIATRIC DISORDERS			
	Insomnia		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Dyspnea		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash acneiform		

[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 Ganetespib trials but with the relationship to Ganetespib still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
EYE DISORDERS - Blurred vision; Eye disorders - Other (transient visual impairment)
GASTROINTESTINAL DISORDERS - Colonic fistula; Gastrointestinal disorders - Other (gastroenteritis)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Infusion related reaction
INVESTIGATIONS - Blood bilirubin increased; Cardiac troponin I increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (blood lactate dehydrogenase increased); Lipase increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hyperkalemia; Hyperuricemia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Pain in extremity
NERVOUS SYSTEM DISORDERS - Syncope
PSYCHIATRIC DISORDERS - Confusion
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough
VASCULAR DISORDERS - Hypertension

Note: Ganetespib 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.

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

Frequency is provided based on 811 patients. Below is the CAEPR for Ziv-aflibercept (VEGF-Trap, AVE 0005).

Version 2.6, November 24, 2015[1]

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

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%)**	
	Pain		
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Wound complication		
	Wound dehiscence		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		
Lymphocyte count decreased			***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		
	Myalgia		***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Headache			***Headache (Gr 3)***
		Ischemia cerebrovascular	***Ischemia cerebrovascular (Gr 2)***
		Reversible posterior leukoencephalopathy syndrome	
		Transient ischemic attack	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Proteinuria		***Proteinuria (Gr 3)***
		Renal disorders - Other (nephrotic syndrome)	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
	Genitourinary system fistula[5]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Pharyngolaryngeal pain		
Voice alteration			***Voice alteration (Gr 2)***

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%)**	
	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) 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.

Safety monitoring for ^{89}Zr-panitumumab PET/CT:

Panitumumab was well tolerated in previous clinical trial studies where doses were much higher. The most common adverse events related to panitumumab at doses of 6 mg/kg every 14 days were skin rash with variable presentation, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea, and diarrhea. The most serious events that have been reported were fibrosis, severe dermatologic toxicity complicated by infectious sequelae and septic death, infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting, and constipation.

No adverse events are expected for the ^{89}Zr-panitumumab PET/CT imaging study. The dose of panitumumab anticipated for this study will be <1 mg for a single injection. The radiation exposure associated with this study is comparable to the dose for the other widely used clinical nuclear medicine procedures.

Subjects will be monitored for adverse events during each ^{89}Zr-panitumumab PET/CT imaging session and for one month post injection. Adverse events are defined as any signs of illness or symptoms that have appeared or worsened since the infusion of the ^{89}Zr-panitumumab. The infusion and imaging procedure will be terminated in any patient who exhibits anaphylaxis, significant hypotension (systolic blood pressure less than 80 mmHg on 2 measurements obtained within 1-2 minutes of each other), dyspnea, or chest pain. At the beginning and end of the imaging session, subjects will be questioned regarding any appearance or change in signs and symptoms. The adverse events to be specifically monitored during the infusion include localized discomfort at the IV injection site, pain, respiratory difficulties, flushing, dizziness, itching/rash, and any other symptoms that could be secondary to anaphylactic reaction. If one participant develops any grade ≥ 2 AE reaction attributable to the imaging agent, the ^{89}Zr-panitumumab study will be placed on hold and discussed with the study sponsor.

Injection site monitoring will be performed prior to administration of the imaging agent and at various time points post-injection over a 24-hr period. Any abnormal findings during this period will be recorded as an AE on the research record. Abnormal injection site findings include, but are not limited to, radiopharmaceutical extravasation, bleeding, hematoma, redness, and infection. Any abnormal finding that is new or represents a worsening from baseline is an AE. Once AE notification is decided upon, the procedure for AE notification will be followed, as described below.

7.3 Adverse Event Characteristics

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

Attribution of the AE:

1. Definite – The AE *is clearly related* to the study treatment.
2. Probable – The AE *is likely related* to the study treatment.
3. Possible – The AE *may be related* to the study treatment.

4. Unlikely – The AE *is doubtfully related* to the study treatment.
5. Unrelated – The AE *is clearly NOT related* to the study treatment.

7.4 Expedited Adverse Event Reporting

7.4.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Expedited Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 7.3.2).

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

7.4.2 Expedited Reporting Guidelines

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

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

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

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.

6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

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

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

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

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" – The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

7.4.3 Protocol-specific expedited AE reporting exclusions

For this protocol only, certain AEs/grades are exceptions to the Expedited Reporting Guidelines and do not require expedited reporting (i.e., CTEP-AERS). These are any grade lymphopenia, any grade alopecia, Grade 2 electrolyte (sodium, potassium, phosphorous, magnesium) abnormalities, Grade 2 anemia, Grade 2 hypoalbuminemia, Grade 2 hyperglycemia, Grade 2 INR, Grade 2 PTT, and Grade 2 hyperuricemia will NOT be reported through CTEP-AERS but will be reported in the routine data submissions.

7.4.4 Pregnancy, Fetal Death, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed for patients who became pregnant on study, and faxed along with any additional medical information to **301-230-0159.** The potential risk of exposure of the fetus to

the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

7.4.4.1 Pregnancy

- Because patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic, DCTD/DCP is requesting that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3** "***Pregnancy, puerperium and perinatal conditions - Other (pregnancy)***" under the ***Pregnancy, puerperium and perinatal conditions*** SOC.
- The pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

7.4.4.2 Fetal Death

- Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."
- Any fetal death should be reported expeditiously, as Grade 4 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions SOC.
- A fetal death should NOT be reported as "Fetal death," a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

7.4.4.3 Death Neonatal

- Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.
- A neonatal death should be reported expeditiously as Grade 4 "General disorders and administration – Other (neonatal loss)" under the General disorders and administration SOC.
- Neonatal death should NOT be reported as "Death neonatal" under the General disorders and administration SOC, a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.

7.4.5 NCI-IRB Expedited Reporting of Adverse Events, Unanticipated Problems, and Deaths

7.4.5.1 Definitions

Adverse event
An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above in Section 7.3.3.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

Suspected adverse reaction
Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse reaction
An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is

not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Serious
An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

Serious Adverse Event
An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Disability
A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse drug experience
Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

Protocol Deviation (NIH Definition)
Any change, divergence, or departure from the IRB-approved research protocol.

Non-compliance (NIH Definition)
The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

Unanticipated Problem
Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
  (b) the characteristics of the subject population being studied; A**ND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.5 NCI-IRB and NCI Clinical Director Reporting Requirements

7.5.1 NCI-IRB Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.5.2 NCI-IRB Requirements for PI Reporting at Continuing Review

For reporting of adverse events at time of continuing review, the NCI-IRB requires a summary report of adverse events that have occurred on the protocol **since the previous continuing review and in aggregate**. The method of presentation should provide the NCI-IRB with the information necessary to clearly identify risks to participants and to make a risk:benefit determination. Please sort the events by the system organ class and by grade. The summary report is based on the following guidance: any unexpected severity and/or unexpected frequency of expected events needs to be reported and interpreted in relation to the risk:benefit of study participants in the narrative.

Please use following table for reporting adverse events at time of CR:

System Organ Class	CTCAE Term	Grade	# of Events since last CR	Total # of Events	Attribution to Research	Serious?	Unexpected?

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

7.5.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that require a sponsor recommended change to the protocol or the consent form or in the opinion of the PI increase risks to study participants will need to be reported to the NCI IRB.

7.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation, or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

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

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

7.7 Second Malignancy

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

8 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational administered in this study can be found in Section 7.

8.1 Ganetespib (NSC 777169)

Other Names:	STA-9090
Chemical Name:	5-[2,4-dihydroxy-5-(1-methylethyl)phenyl]-2,4-dihydro-4-(1-methyl-1*H*-indol-5-yl)-3*H*-1,2,4-triazole-3-one
Classification:	Hsp90 inhibitor
CAS Registry No.	888216-25-9
Mode of Action:	Ganetespib inhibits heat shock protein 90 (Hsp90) chaperone activity by binding to its N-terminal adenosine triphosphate pocket resulting in the proteosomal degradation of oncogenic client proteins. Client protein degradation results in induction of cell cycle arrest and apoptosis, thereby inhibiting tumor growth.
Mol. Formula:	$C_{20}H_{20}N_4O_3$
Mol. Weight:	364.40 g/mol
Description:	Ganetespib is a novel triazolone heterocyclic compound, provided as a concentrate solution and is a clear, colorless-to-pale-yellow solution.
How Supplied:	Synta Pharmaceuticals supplies ganetespib and PMB, CTEP, DCTD distributes as 300 mg vials, 25 mg/mL, (total volume is 12.84 mL with 0.84 mL overfill). The solution is a clear, colorless-to-pale yellow solution free of visible particles in a polyethylene glycol 300, polysorbate 80 and dehydrated alcohol cosolvent-surfactant system.
Storage:	The 300 mg vials should be stored at 20°C - 25°C (68°F – 77°F) with excursions allowed between 15°C and 30°C (59°F and 86°F) (USP Controlled Room Temperature), protected from light.
Stability:	Stability of the intact vials is ongoing. If not used immediately, store the prepared IV solution at controlled room temperature, protect from light. Do not refrigerate the IV solution. The IV solution is to be administered over 1 hour and must be completed within 4 hours of finishing the preparation.
Preparation:	Use an empty non-PVC and non-DEHP IV bag to prepare ganetespib IV solution to a final concentration between 0.1 and 1.1 mg/mL. For consistency, 500 mL D5W should be the final volume of the prepared IV

1. Add the calculated volume (mL) of D5W into the non-PVC, non-DEHP empty IV bag
2. Next, add the calculated amount (mL) of ganetespib. Note: ganetespib solution is viscous. Use a 16G or 18G needle to withdraw the calculated amount of ganetespib.
3. Gently invert the IV bag approximately 10 times to completely mix the IV solution
4. Visually inspect the final IV solution. The solution must be clear and free of visible particles. Do not use it if the IV solution is not clear.

Route of Administration: Intravenous.

Method of Administration: 1. Set up the infusion pump to deliver the 500 mL ganetespib infusion solution over 60 minutes.

Note: Use of Vascular Access Devices: Based on preclinical data, use of vascular access devices (VADs) (such as ports and peripherally-inserted central catheters [PICCS]) containing silicone catheters are permitted. Use of VADs with catheters made of any material other than silicone is not allowed.

Following ganetespib administration through a VAD, care should be taken to flush the line after each dose of study drug. Please follow routine clinical practice for care of patients utilizing VADs.

2. At the end of the infusion, the IV tubing **must be flushed with D5W** to ensure complete delivery of the required dose of ganetespib. The infusion rate of the D5W flush should be at the same rate as the drug infusion.

3. Dispose of used IV bags, tubing and used drug vials per institutional guidelines.

Potential Drug Interaction: In vitro and in vivo, ganetespib is primarily metabolized (glucuronidated) by UGT1A9 and to a lesser extent by UGT1A1, UGT1A3, and various P450 enzymes. It is also a substrate for P-glycoprotein, but is primarily eliminated through glucuronidation. In vitro, ganetespib is a moderate inhibitor of CYP2C19 and CYP3A4, but has not demonstrated any clinically significant drug interactions to date, including a study of its effect on omeprazole (a sensitive CYP2C19 substrate) pharmacokinetics in healthy human volunteers. Avoid concomitant administration with moderate or strong UGT1A9 inhibitors, which include efavirenz and propofol. The concomitant use of inducers of UGTs (e.g., rifampin, phenobarbital, phenytoin, various herbal preparations including St. John Wort) might significantly increase ganetespib clearance, resulting in reduced plasma concentrations.

	The QTc study in healthy volunteers has reported a modest increase in QT interval 24 hours post ganetespib dose. To date, clinical experience with ganetespib does not support an evidence of a clinical safety risk for QTc interval prolongation and Torsade de Pointes or other uncontrolled arrhythmias. However, until the effect of ganetespib on QT interval is completely characterized, patients should avoid concomitant drugs that may cause QTc interval prolongation while receiving ganetespib, see Appendix C.
Availability	Ganetespib is an investigational agent supplied to investigators by DCTD, NCI. Ganetespib is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and DCTD, NCI.

8.2 Ziv-aflibercept (NSC 724770)

Other Names:	AVE0005; Zaltrap
Classification:	Recombinant humanized fusion protein (Chinese hamster ovary source)
Mode of Action:	The cytokine VEGF binds to and activates VEGFR1 and VEGFR2 on the vascular endothelium, promoting new vessel formation. VEGF Trap is a soluble recombinant decoy receptor that binds and inactivates extravascular and hematologic VEGF. It reduces tumor vasculature density, available nutrient supply, and tissue matrix components escaping from leaky tumor vessels.
Molecular Weight:	115 kDa
Approximate Solubility:	At least 100 mg/mL water (with 5mM Na phosphate, 5 mM Na citrate, 100 mM NaCl, 0.004-0.08% Polysorbate 20) at 5°C and 25°C.
Description:	The fusion protein ziv-aflibercept (VEGF Trap) is comprised of 2 portions of human VEGF receptor extracellular domains, VEGFR1 and VEGFR2, fused to the Fc portion of human IgG1.
How Supplied:	Ziv-aflibercept (VEGF Trap) is supplied by Sanofi-Aventis Pharmaceuticals and distributed by CTEP, DCTD, NCI. Ziv-aflibercept (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 dehydrate, citric acid monohydrate, polysorbate 20, sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, and water for injection. The pH of ziv-aflibercept (VEGF Trap) is 6.2. The product is packaged in a type 1, clear borosilicate glass vial closed with a flanged cap with tear-off lid and inserted sealing disc, Flurotec® (PTFE) coated.
Preparation:	Prior to infusion, the VEGF Trap dosage form must be diluted directly

	into infusion bags of 0.9% sodium chloride solution or 5% dextrose. The concentration of the diluted solution can range between 0.6 and 8 mg/mL. The pH of the diluted solution is about 6.2.
Storage:	Intact vials are stored at 2°C to 8°C (Refrigerated condition).
Stability:	Shelf-life stability studies of intact vials are ongoing. Ziv-aflibercept's provisional shelf-life is up to 36 months at 2°C to 8°C. *Caution: The sterile single use vials contain no antibacterial preservatives. Discard remaining agent 8 hours after initial entry*. Ziv-aflibercept (VEGF Trap) diluted to a concentration of 0.6 to 8 mg/mL in 0.9% NaCl or 5% dextrose has demonstrated chemical and physical stability for up to 24 hours under refrigerated conditions (2°C to 8°C) or up to 8 hours at ambient temperature (approximately 25°C) in infusion bags made of polyvinyl chloride (PVC) containing di(2-ethylhexyl)phthalate (DEHP) or polyolefin (PVC free DEHP free), or polyethylene.
Route of Administration:	Intravenous
Method of Administration:	Administer ziv-aflibercept (VEGF Trap) intravenously over 1 hour into a peripheral vein or central venous catheter using gravity, an infusion pump, or syringe pump. The infusion should not exceed two hours at room temperature (approximately 25°C). Ziv-aflibercept (VEGF Trap) may be administered using infusion tubing made of PVC containing DEHP, polyethylene lined PVC, DEHP free PVC containing tris (2-ethylhexyl) trimellitate (TOTM), polypropylene, or polyurethane, or polybutadiene. The infusion set must contain a 0.2 micron polyethersulfone inline filter. Polyvinylidene fluoride (PVDF) filters or Nylon filters should **not** be used.
Availability	Ziv-aflibercept is an investigational agent supplied to investigators by DCTD, NCI. Ziv-aflibercept is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and DCTD, NCI.

8.3 89Zr-labeled Panitumumab

Other Names:	[^{89}Zr]-DFO-panitumumab or ^{89}Zr-panitumumab
Classification:	Radiopharmaceutical for imaging
IND#:	Cross reference support from IND 116229, held by DCTD/CIP
Composition:	Fully human IgG2 monoclonal antibody

Mechanism of Action:	Panitumumab competes with endogenous ligands such as epidermal growth factor and tumor growth factor α (TGF α) to block stimulation of the EGF receptor. By blocking the ligand-receptor interaction, critical signaling cascades are prohibited from occurring which would otherwise result in downstream activation of signaling pathways involved in the progression of metastatic disease. Some of these processes include: cell growth, survival, motility, proliferation, and transformation.
How Supplied:	^{89}Zr-panitumumab is a sterile, IV injectable solution with a volume of ≤10 mL containing 0.9% saline and <5 mg gentistic acid.
Storage:	Vials are stored at 2°C to 8°C (36°C to 46°F) (refrigeration conditions) until time of use. Protect from direct sunlight exposure. Do not freeze.
Route of Administration:	The agent is administered by intravenous injection, not to exceed 1.0 mCi, of ^{89}Zr-panitumumab. Appropriate shielding to meet Radiation Safety Guidelines will be used.

Toxicity: Panitumumab was well tolerated in previous clinical trials studies where doses were much higher. The most common adverse events related to panitumumab, at doses of 6mg/kg every 14 days, were skin rash with variable presentation, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea, and diarrhea. The most serious events that have been reported were fibrosis, severe dermatologic toxicity complicated by infectious sequelae and septic death, infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting, and constipation.

NOTE: For PET imaging purpose we will be using panitumumab labeled with ^{89}Zr. ^{89}Zr-labeled, EGFR-targeting antibody panitumumab is expected to be administered as a microdose. A microdose is defined as less than 1/100th of the dose calculated to yield a pharmacological effect of a test substance, or, for proteins, not more than 30 nanomoles. In this trial, we propose administering <1 mg of panitumumab, which is approximately 1/500th (0.2%) of the recommended therapeutic (pharmacologic) dose of 6 mg/kg, less than 7 nmol. Microdose studies are designed to evaluate the pharmacokinetics or imaging of specific targets and are not designed to induce pharmacological effects. Thus, the potential risk is very low and information adequate to support the initiation of such limited studies can be derived from limited pre-clinical safety studies.

Safety monitoring for ^{89}Zr-panitumumab PET/CT: Panitumumab was well tolerated in previous clinical trial studies where doses were much higher. The most common adverse events related to panitumumab at doses of 6 mg/kg every 14 days were skin rash with variable presentation, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea, and diarrhea. The most serious events that have been reported were fibrosis, severe dermatologic toxicity complicated by infectious sequelae and septic death, infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting, and constipation.

No adverse events are expected for the ^{89}Zr-panitumumab PET/CT imaging study. The dose of panitumumab anticipated for this study will be <1 mg for a single injection. The radiation

exposure associated with this study is comparable to the dose for the other widely used clinical nuclear medicine procedures.

A 5-mL blood sample will be drawn for immunogenicity testing prior to initial ^{89}Zr panitumumab administration and during Cycle1 Day 16. Samples will be delivered at room temperature to Building 10/IB54 for appropriate testing.

Drug Interactions: There are no formal evaluations regarding drug-food, drug-lab, or drug-disease interaction that are currently available.

Production of the Radiopharmaceutical: The ^{89}Zr-panitumumab used in this study is prepared locally by the Leidos Biomedical Research Radiopharmacy, Frederick, MD. The precursors for the radiosynthesis include panitumumab, deferoxamine-NCS, and ^{89}Zr-oxalate. The other reagents used in the synthesis are sodium carbonate, water, gentisic acid, HEPES, and USP saline for injection. The radiopharmaceutical product is a clear and colorless liquid that is stored at room temperature in a sterile serum vial. ^{89}Zr-panitumumab has an expiration time of 48 hours after sterile filtration.

8.4 Agent Ordering

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

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.

Agent Ordering for ^{89}Zr-panitumumab: ^{89}Zr-panitumumab will be ordered from the Leidos Biomedical Radiopharmacy using the form supplied in Appendix D; orders should be placed 5 business days prior to the scheduled scan date and time.

George Afari, PharmD, BCNP
Clinical Radiopharmacist
Applied/Developmental Research Directorate, Leidos Biomedical Research, Inc.
Frederick National Laboratory for Cancer Research
Phone: 301 846 7391
Fax: 301 846 5935
E-mail: george.afari@nih.gov

8.5 Agent Accountability

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

Agent Accountability for ^{89}Zr-panitumuab: The organic precursor for ^{89}Zr-panitumumab is purchased commercially in single-use, 200-mg vials that are delivered to the custody of Dr. George Afari, the lead nuclear radiopharmacist for this project. They are stored in a controlled temperature refrigerator in a locked and secure room and they are inventoried with a chain of custody maintained from the time of receipt. Each radiosynthesis is done by Dr. George Afari or his designee and, after passing all required quality control assays, the product ^{89}Zr-panitumumab dose is drawn up under the supervision of Dr. George Afari or the nuclear medicine physician investigators Dr. Peter Choyke, Dr. Karen Kurdziel, or Dr. Liza Lindenberg.
The quality control tests that must be passed prior to release of the product ^{89}Zr-labeled, EGFR targeting antibody panitumumab for injection include radioactive purity, radiochemical purity, pH, sterilizing filter integrity, and tests for endotoxin and particulates. The dose is drawn up into a syringe, assayed for mCi at time of injection, labeled, and administered to the research subject.

Agent Returns: If for any reason the study imaging is unable to be completed, sites will allow the radioactivity of the ^{89}Zr-panitumumab solution to decay and then discard it appropriately per site's policies and procedures, making a record of the event as required. A copy of the policy should be available upon request.

9 CORRELATIVE/SPECIAL STUDIES

We plan to evaluate the effect of modulation of HIF1α inhibition and additional Hsp90 client proteins as a result of combination therapy with ganetespib and ziv-aflibercept. We also plan to pursue ^{89}Zr-panitumumab PET/CT imaging to evaluate tumor distribution of EGFR prior to and following treatment with both agents as an exploratory correlation for evidence of modulation of EGFR, as an indirect biomarker of Hsp90 inhibition, as EGFR is a known Hsp90 client protein.

Two core biopsies will be obtained, one on C1D7 prior to administration of ganetespib on C1D8, and 7 days after administration of ziv-aflibercept on C1D1; and again on C2D7, 7 days after treatment with the combination of ganetespib and ziv-aflibercept on C2D1, but before administration of ganetespib on C2D8. One core will be immediately flash frozen for analysis of HIF1α, a second core will be stored and later analyzed for Hsp90 client proteins based on the availability of tissue and various histologies, and availability of assays.

Circulating tumor cells (CTCs) will be isolated from whole blood samples collected at baseline and then throughout the study for assessment of DNA damage response markers such as γH2AX. These samples will be optional and will be collected from patients on the MTD expansion phase only. We will also evaluate whether we can measure changes in the number and phenotype (epithelial-mesenchymal transition) of CTCs in patients over time to explore any correlation with response to treatment or disease progression. This analysis will be performed in Dr. Kinders' lab with the ApoStream instrument, which uses antibody-independent CTC isolation technology that can isolate viable CTCs from epithelial and non-epithelial cancers. The enriched cells are then stained with a panel of antibodies targeting MUC1 (tumor marker) and CEA (tumor marker), CK (epithelial marker), EpCAM (epithelial marker) and β-catenin (CTNNB1; epithelial-mesenchymal transition marker) and CD45 (PTPRC; leukocyte marker), as an exclusion marker.

9.1 Pharmacodynamic Assays

Assessment of HIF1α protein expression in tumor biopsies:

To determine whether the combination of ganetespib and ziv-aflibercept modulates intra-tumoral HIF1α expression, tumor biopsies will be analyzed for change in HIF1α expression by immunofluorescence assay (IFA). Cores will be normalized against the percentage of tumor within the sample. Paired pre- and post-combination treatment samples will be compared for qualitative changes in levels of HIF1α expression.

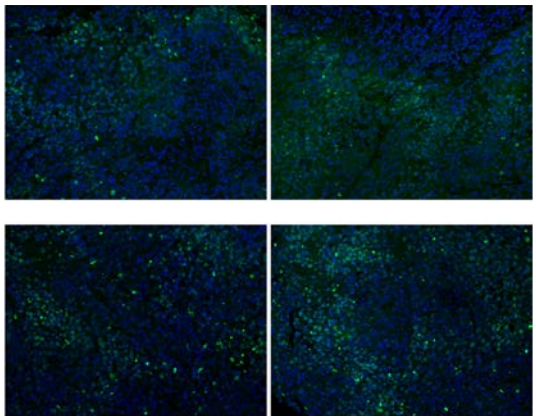

Figure 6. IFA showing HIF1α expression in A375 xenograft tumors treated for 2 hours with topotecan and counterstained with DAPI.

Assessment of EGFR modulation by ^{89}Zr-panitumumab PET/CT imaging:

To evaluate for tumor distribution of EGFR, patients will undergo ^{89}Zr-immuno-PET imaging with ^{89}Zr-labeled EGFR-targeting panitumumab antibody in all patients as a non-invasive exploratory correlative to evaluate modulation of EGFR client protein prior to and after treatment with the combination of ganetespib and ziv-aflibercept. Immunohistochemistry staining to confirm EGFR expression in archival tumor biopsies will be performed prior to pursuing scans. Panitumumab is a fully human monoclonal antibody that targets EGFR and competes with endogenous ligands to block stimulation of EGFR. ^{89}Zr-immuno-PET imaging with panitumumab as a targeting ligand allows for quantification of EGFR expression within tumors. Changes in ^{89}Zr-panitumumab PET/CT avidity (as measured by SUV) can therefore serve as a surrogate biomarker of Hsp90 inhibition, as EGFR is a known Hsp90 client protein.

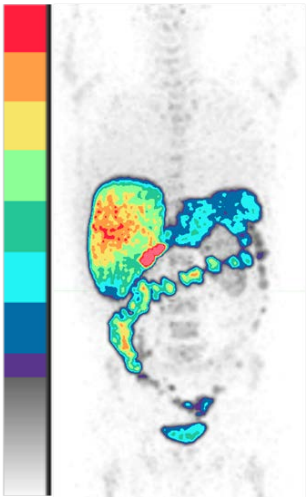

Figure 7 Example of Zr89 Panitumumab scan from a patient with colon cancer metastasis to the liver. Note the high physiologic radiotracer activity in the liver with decreased uptake in metastatic lesions.

9.1.1 Laboratory Contact

At least 24 hours prior to tumor biopsy or blood sample collection, the research nurse will contact the NCI Phase I/II PK/PD Support Group in NIH Building 10: E-mail NCIPK-PDsupportgroup@mail.nih.gov, Pager: 102-12798 Phone: 301-451-1169 Fax: 301-480-5871. For biopsies, tubes pre-labeled with the information specified in Section 9.1.4, biopsy date, and site of tissue biopsy will be provided. Initial processing and shipping of the samples will be completed as described below.

9.1.2 Tumor Biopsies

9.1.2.1 Timing of tumor biopsies

Biopsies will be mandatory during the expansion phase. Biopsies will be collected at the following time points:

- On C1D7 before ganetespib administration on C1D8 (baseline)

- On C2D7 after combination of ganetespib and ziv-aflibercept on C2D1, and before ganetespib administration on C2D8

If tumor biopsies are pursued, the first dose of ganetespib on C1D1 will be omitted.

9.1.2.2 Biopsy Procedure

Serial tumor biopsies will be obtained by the Interventional Radiology team by a percutaneous approach. It is preferred that 2-3 core biopsies 18-gauge in diameter and ≥1 cm in length will be obtained during each procedure. It is estimated that there will be between 2 million–5 million cells from each biopsy. If a site is deemed appropriate for biopsy with minimal risk to the participant by agreement between the investigators and Interventional Radiology team, an attempt for biopsy will be made.

The use of imaging to facilitate biopsies will be decided by members of the Interventional Radiology team and may include ultrasound, CT scan, or MRI. Should a CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. Tumor biopsies and local anesthesia will be administered only if they are considered to be of low risk to the participant, as determined by the investigators and Interventional Radiology.

If the participant chooses not to undergo tumor biopsy, he/she will still remain in the study and receive study medication, and all the other correlative studies will be performed.

Tumor biopsies are optional during the escalation phase and mandatory during the expansion phase. Baseline biopsies will be performed following patient enrolling on study. If an initial attempt at percutaneous biopsy is unsuccessful, the patient will be given an option to proceed with a repeated attempt at percutaneous biopsy. A separate consent form must be signed for each biopsy procedure, so patients may choose not to undergo subsequent biopsies. If the baseline biopsy is unsuccessful or the patient refuses to undergo subsequent biopsies, no further biopsies will be performed but the patient will remain on study, receive study medication, and other correlative studies will be performed.

9.1.2.3 Solid Tumor Biopsy Processing

At least two tissue cores will be collected. The cores will be transferred into a 1.5-mL pre-chilled cryovial and then flash frozen in liquid nitrogen per DCTD SOP340507 (http://dctd.cancer.gov/ResearchResources/biomarkers/docs/par/SOP340507_Biopsy_Frozen.pdf). Samples will be submitted to Dr. Kinders' laboratory for evaluation of DNA damage markers, and H&E pathology evaluation. The frozen biopsy specimens are transferred to PADIS on dry ice, where the core biopsy samples are stored at -80°C, or colder, and

subsequently processed within 7-10 days for analysis or as directed by the Principal Investigator. Biopsy samples will be analyzed for HIF1α expression as described above; any additional cores will be flash-frozen and kept for future analysis in the Frederick National Laboratories CR Biorepository in liquid nitrogen freezers.

Biopsies for PD analysis will be shipped on dry ice to Dr. Kinders' laboratory:

Dr. Robert Kinders (PADIS/LHTP/FNLCR)
Bldg. 431, Rm. 129
Frederick, MD 21702-1201
Phone: 301-846-6410
kindersr@mail.nih.gov

9.1.3 Circulating Tumor Cells

Whole blood for CTCs will be collected aseptically by venipuncture or from a venous port into two K3 EDTA 4 mL tubes. Samples will be collected at the following times from patients on the expansion cohort only:

- cycle 1 prior to drug administration
- cycle 1 day 8 (+/- 1 day, i.e., prior to the administration of ganetespib on C1D8)
- cycle 1 day 5, 4 hours (+/- 1 hour) after completion of drug administration
- cycle 2 day 8 (+/- 1 day, i.e., prior to the administration of ganetespib on C2D8)
- cycle 2 day 15, 4 hours (+/- 1 hour) after completion of drug administration
- on day 1 of all subsequent cycles before drug administration

One additional blood sample will be collected at time of disease progression. All CTC samples will be shipped to Dr. Kinders' lab.

9.1.4 Sample Collection and Processing

Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and patient confidentiality pursuant to informed consent provisions. Information about each specimen (e.g., blood, tumor biopsy, circulating tumor cells, per specific protocol) will be recorded on a PK/PD collection worksheet.

Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. To ensure patient confidentiality, only containers used for the initial specimen collections will be labeled with patient identifiers.

Only the barcode identifier will be applied to all subsequent specimen containers. When specimens are processed and aliquoted, no patient information will be

included on the new containers. Original specimen containers will be discarded. Only barcode-labeled specimens without patient identifiers will be shipped for analysis and/or storage. Specimen labels will indicate: CTEP protocol number, unique patient accession number, 3-digit sample number (see list below), collection time, and total volume collected, as appropriate. Samples from sets of at least three patients will be grouped for scientific analysis.

Standardized 3-digit sample collection numbers:
400 series: blood for circulating tumor cells (CTCs)
500 series: tumor biopsies

The inventory process contains other security provisions sufficient to safeguard patient privacy and confidentiality. Access to the inventory system and associated documents will be restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved. The only patient information available in the inventory system will be the patient sex, diagnosis, and level of informed consent given. SOPs ensure that any changes in informed consent made by a patient and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to SOPs and will be monitored for high-quality performance.

Any new use of these samples will require prospective IRB review and approval. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e., broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

9.1.5 Immunohistochemistry

Patients undergoing ^{89}Zr-panitumumab PET/CT scans will be required to submit a minimum of 2 unstained slides from archival tumor biopsies to the Laboratory of Pathology, CCR, NCI for confirmation of EGFR expression by immunohistochemistry (IHC) to determine eligibility prior to undergoing scans. IHC staining for EGFR will be performed using the commercially available mouse anti-EGFR antibody from Zymed Laboratories, (Zymed Laboratories, Inc., Invitrogen Immunodetection, South San Francisco, CA) according to the manufacturer's instructions. Positivity will be defined as any membrane staining for EGFR in tumor cells. For enrollment purposes the archival material will be scored solely as positive or negative. Only those patients whose tumors are scored

as positive will be eligible for ^{89}Zr-panitumumab scans; scans are optional during the escalation phase and mandatory during the expansion phase of this trial.

9.1.6 Imaging Studies

We are conducting ^{89}Zr-immuno-PET imaging with panitimumab as a targeting ligand in the 10 patients enrolled in the expansion cohort, scans are optional during the escalation phase. ^{89}Zr-panitumumab will be administered at baseline (prior to cycle 1 day 1 of treatment) and PET/CT imaging will be performed 2-6 hours following ^{89}Zr-panitumuab injection. If uptake into tumors is shown to be measurable, a second ^{89}Zr-panitumumab infusion and scan will be performed at the end of cycle 1. Uptake of ^{89}Zr-panitumumab in normal tissue and tumors will be evaluated and human dosimetry values will be calculated.

^{89}Zr-panitumumab PET/CT will be performed in the NCI Molecular Imaging Clinic (B3B). The injectable dose of ^{89}Zr-panitumumab for this study will be 1.0 mCi (37 MBq), with an allowable range of 0.75 to 1.0 mCi (28-37 MBq), and with a specific activity greater than 200 Ci/mmol at the time of injection. The injected mass dose is less than or equal to 1 mg (7 nmol). Ordering instructions for ^{89}Zr-panitumumab are provided in Appendix D. Participants with severe claustrophobia not relieved by oral anxiolytic medication or patients weighing >136 kg (weight limit for scanner table) may not undergo ^{89}Zr-panitumumab imaging. ^{89}Zr-panitumumab is a sterile, IV injectable solution that will be administered to subjects over 1 minute by intravenous bolus injection.

The infusion and imaging procedure will be terminated in any patient who exhibits anaphylaxis, significant hypotension (systolic blood pressure less than 80 mmHg on 2 measurements obtained within 1-2 minutes of each other), dyspnea, or chest pain.

9.1.6.1 Scanning Procedure

The scanning acquisition should include the patient torso, from the mid-ears to the mid-thighs. A corresponding low energy transmission CT will be acquired immediately before each emission scan for attenuation correction and localization purposes. The acquisition time for each PET/CT image is estimated at one hour. The injected dose of ^{89}Zr-panitumumab will not exceed 1.0 mCi. The minimum injected dose will be 0.75 mCi, although the total dose administered may be reduced at the discretion of the principal investigator on a case-by-case basis due to unpredictable delays. The reasoning for a reduction in the dose will be clearly documented.

9.1.6.2 Image Analysis

- Preliminary analysis will be performed to define human dosimetry and evaluate tumor uptake/image quality (as determined by an experienced nuclear imaging physician).

- The uptake within an EGFR positive tumor us expected to be greater than mean background activity + 2X the standard deviation of the background tissue.
- Regions/Volumes of interest (VOIs) will be drawn within the tumor focus/foci and normal solid organs, which will be identified on the transmission CT scan. For the tumor foci, an estimated smoothed maximum standard uptake value (SUV; SUV_{max}) will be reported as the mean SUV value of an automated 80% maximum pixel value threshold based on volume of interest (i.e., the average SUV of the :hottest" 20% of pixels in the user defined lesion). This method reduces the chances of the SUV_{max} value being dominated by one or more "noisy" pixel values. Additional VOIs will include an anatomic value based on the transmission CT and a metabolic volume using an absolute SUV_{max} threshold. For the normal solid organs, VOIs will also be drawn and SUV_{mean} will be reported.
- A small VOI will also be defined within the left ventricular or atrial cavity or over the aorta to obtain the blood pool and SUVmean will be reported.
- A normal tissue "background" VOI will be drawn by establishing a 50% maximum pixel value volume of interest (VOI), drawn within a homogeneous non-tumor-involved region within the organ in which the tumor resides. This VOI will be used to determine tumor:background ratios.
- All regions/volumes of interest will be saved. Region volumes, and SUV values will be output to an Excel spreadsheet using MIM imaging software (www.mimsoftware.com)
- Image data will be used to calculate the dosimetry using OLINDA (Organ Level Internal Dose Assessment Code, sopyright Vanderbilt University, 2003) software and to obtain preliminary tissue uptake variability measurements

9.1.6.3 Data Analysis

SUV_{max} and SUV_{mean} within the tumor and non-tumor areas, and tumor:background will be analyzed. Percent change of SUV between baseline and after the first cycle will be assessed. Based on published PET/CT reproducibility data, a percent change >20% in SUV values will be considered significant.

9.1.7 Human Data Sharing Plan

What data will be shared?
We will share human data generated in this research for future research as follows:
X De-identified data in an NIH-funded or approved public repository
X Identified data in BTRIS (automatic for activities in the Clinical Center)
X De-identified or identified data with approved outside collaborators under appropriate agreements

How and where will the data be shared?
Data will be shared through:
X An NIH-funded or approved public repository: clinicaltrials.gov

X BTRIS (automatic for activities in the Clinical Center)
X Approved outside collaborators under appropriate individual agreements
X Publication and/or public presentations

When will the data be shared?
X At the time of publication or shortly thereafter

10 STUDY CALENDAR

Baseline evaluations are to be conducted within 72 hours prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. Start of next cycle may be delayed for up to 1 week to accommodate scheduling conflicts. Treatments within a cycle may be delayed up to +/- 1 day to accommodate scheduling conflicts. History and physical examination and laboratory evaluations can be performed up to 3 days before the start of the next cycle.

Study Procedure	Screen	Study Treatment								
		Cycle 1				Cycle 2 and subsequent cycles				Off Treatment
		W1	W2	W3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4	
Ganetespib[a]		X[b]	X	X		X	X	X		
Ziv-Aflibercept		X		X		X		X		
Informed consent	X									
Demographics	X									
Medical history	X									
Concurrent meds	X	X----------							X	
Physical exam[d]	X		X	X		X	X	X		X
Vital signs[d]	X		X	X		X	X	X		X
Height[d]	X									
Weight[d]	X		X	X		X	X	X		X
Performance status[d]	X		X	X		X	X	X		X
CBC w/diff, plts[e]	X		X	X		X	X	X		X
Serum chemistry[e]	X		X	X		X	X	X		X
Urine protein/creatinine[e]	X			X		X		X		X
PT, INR, PTT[f]	X		X				X			
β-HCG[g]	X									
Electrocardiogram[h]	X	X	X	X		X	X	X		
Echocardiogram[i]	X									
Ophthalmologic exam[j]	X									
Adverse event evaluation	X	X----------							X	
Tumor measurements	X	Tumor measurements are repeated every 2 cycles. Documentation (radiologic) must be provided for patients removed from study for progressive disease.								X
Tumor biopsy[k]			X				X			
^{89}Zr-panitumumab PET/CT scan[l]		X		X						
PD blood collection[m]	X	X	X			X	X			

a. Ganetespib will be administered intravenously on D1, 8, and 15 of a 28-day cycle.

b. In order to accommodate biopsies, D1 administration of ganetespib may be omitted during cycle 1 only.

c. Ziv-aflibercept will be administered intravenously on D1 and 15 of a 28-day cycle.

d. Physical examination, including vitals, weight, and performance status, will be performed at the Clinical Center at the start of each cycle or treatment (up to 3 days before start of a new cycle or treatment). Height will be performed at enrollment and will not need to be repeated prior to each treatment.

e. Serum chemistry (albumin, total bilirubin, calcium, creatinine, phosphorus, magnesium, potassium, sodium, SGOT [AST], SGPT [ALT], amylase, lipase); CBC w/diff, and platelets should be performed within 72 hours of enrollment and weekly thereafter on weeks of treatment, prior to the first treatment of that week. If clinically indicated, labs may be obtained with more frequency with subsequent cycles. Urine protein/creatinine ratio will be checked prior to treatment with ziv-aflibercept.

f. PT/INR, PTT prior to biopsy.

g. Serum pregnancy test (women of childbearing potential) within 1 week prior to enrollment and as clinically indicated.

h. Electrocardiogram will be performed prior to each ganetespib treatment and approximately 24 hours after each treatment during the first cycle, and will be repeated as indicated until QTc is less than 500 msec. With subsequent cycles, electrocardiogram will be performed prior to each treatment, and repeated after treatment if clinically indicated.

i. Echocardiogram must be performed within 4 weeks prior to enrollment and as clinically indicated thereafter.

j. Ophthalmologic exams must be performed within 4 weeks prior to enrollment and as clinically indicated thereafter.

k. Tumor biopsies will be obtained on Cycle 1 D7 prior to administration of ganetespib on C1D8, and again on C2D7 before administration of ganetespib on C2D8. Tumor biopsies are optional during the escalation phase and mandatory during the expansion phase. If tumor biopsies are collected, the first dose of ganetespib on C1D1 will be omitted.

l. ^{89}Zr-panitumumab scan will be performed in patients with confirmed EGFR expression on archival tumor tissue prior to initiation of treatment on C1D1. If there is evidence of measurable uptake on baseline scans, patients will receive a second ^{89}Zr-panitumumab PET/CT scan after completion of C1D15 treatment, on C1D16 ± 1 day. If patients are unable to have a second scan during cycle 1 due to scheduling conflicts, scans may be performed during C2D16 ± 1 day. Scans will be optional during the escalation phase and mandatory during the expansion phase.

m. Blood for circulating tumor cells (optional) will be collected on the expansion phase only per Section 9.1.3

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated for response every 8 weeks (every 2 cycles). In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

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

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with the combination of ganetespib and ziv-aflibercept.

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

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

11.1.2 Disease Parameters

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

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and

abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

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

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

11.2 Guidelines for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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

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

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

As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

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

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

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

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

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

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

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

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

11.3 Response Criteria

11.3.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.3.2 Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

11.3.3 Evaluation of Best Overall Response

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

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

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

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

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.4 Duration of Response

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

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

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

12 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (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). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Note: **All** adverse events that have occurred on the study, including those reported through CTEP-AERS, must be reported via the monitoring method identified above.

12.1.2 Responsibility for Data Submission

N/A

12.2 CTEP Multicenter Guideline

N/A

12.3 Collaborative Agreements Language

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

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

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

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

   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as

described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

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

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

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

   E-mail: ncicteppubs@mail.nih.gov

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

13 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This Phase I study will use a standard 3+3 design. The MTD dose for the combination of ganetespib and ziv-aflibercept is defined as the dose level at which no more than 1 of 6 patients experience a DLT during the first cycle of the treatment, and the dose level below that at which at least 2 (of < 6) patients have DLT as a result of the drug. Patients will

receive ganetespib intravenously on a weekly basis, on days 1, 8, and 15, for 3 weeks out of 4, every 28 days, and ziv-aflibercept intravenously every 2 weeks, on days 1 and 15, during a 28-day cycle. Once the MTD is established, 10 additional patients will be enrolled to the expansion phase of the trial, at the MTD and tumor biopsies will be obtained to assess for pharmacodynamic endpoints. Patients will also undergo an ^{89}Zr-panitumumab PET/CT scan to evaluate tumor distribution of EGFR prior to and following treatment with both study agents.

13.2 Sample Size/Accrual Rate

We plan to accrue a total of 22 patients in this study. To allow for some patients who may have only evaluable and not measurable disease, the accrual ceiling is set at 26. It is anticipated that 2-3 patients may be enrolled per month onto this study. It is expected that 14-21 months will be required to accrue the number of patients necessary to complete the trial.

13.3 Analysis of Secondary Endpoints

At the maximal tolerated dose (MTD), we will enroll an additional 10 patients, with mandatory tumor biopsies, for further assessment of pharmacodynamics and imaging endpoints. HIF1α expression and EGFR expression (as measured by SUV, using ^{89}Zr-labeled, EGFR-targeting panitumumab antibody PET/CT imaging) will all be assessed similarly, in an exploratory fashion. For each endpoint, the mean difference (or mean log-difference, if such a transformation appears appropriate) between pre- and post-treatment values, paired by patient, will be assessed by the 1-sample paired t-test, at the 1-sided .05 significance level, if the differences (or log-differences) appear distributed in approximately normal (uni-modal) fashion. This test will have 90% power to detect a treatment related change, in any individual endpoint, equivalent to approximately 0.92SD associated with the natural variation over repeated measures in the absence of treatment. If the differences are not distributed in approximately normal (uni-modal) fashion, the non-parametric sign test will be used to assess whether the observed treatment related changes are in a reliably negative direction (this test will have low power, since it requires that at least 8 of the 10 changes be in the negative direction, to achieve statistical significance at the 1-sided .05 level).

14 HUMAN SUBJECTS PROTECTIONS

14.1 Justification for Subject Selection

This study will be open to all individuals regardless of gender, ethnicity, or race, provided that the aforementioned inclusion and exclusion criteria are met. Patients for this study will be recruited through internal referral, our physician referral base, and through various cancer information hotlines (i.e., Clinical Studies Support Center, 1-800-4Cancer). To date, there is no information that suggests that differences in drug metabolism or effect on

tumor would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but a balance must be struck between participant safety considerations and limitations on the number of individuals exposed to potentially ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, a follow-up study may be written to investigate those differences more fully.

Due to lack of knowledge of the effects of the combination of ganetespib and ziv-aflibercept on the fetus or infants, as well as the possibility of teratogenic effects, pregnant and nursing women will be excluded from this trial. Patients with unstable or serious medical conditions are excluded due to the possibility that the combination of ganetespib and ziv-aflibercept may worsen their condition and the likelihood that the underlying condition may obscure the attribution of adverse events to ganetespib and ziv-aflibercept. HIV-positive patients on combination antiretroviral therapy are excluded from the study because of possible PK interactions with the combination of ganetespib and ziv-aflibercept.

14.1.1 Participation of Children

This study includes patients 18 years of age and older. Because insufficient dosing or adverse event data are currently available on the use of combination of ganetespib and ziv-aflibercept in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials. Studies will be performed in patients <18 years of age when it is appropriate to do so.

14.2 Evaluation of Benefits and Risks/Discomforts

There may or may not be any clinical benefit to a patient from participation in this trial. Their participation will benefit future cancer patients. Potential risks include the possible occurrence of any of a range of side effects that are listed in the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients as described in Section 5 and Section 6. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which participants are entitled under applicable regulations.

14.3 Consent and Assent Process and Documentation

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, drug administration plan, research objectives, and follow-up of this trial. The patient will be provided an IRB-approved consent for review and signature and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient. The original signed consent goes to Medical Records; a copy will be placed in the research record.

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on study.

14.4 Procedure for Protecting Against or Minimizing Any Potential Risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients, which are currently unforeseeable. All patients will be monitored for side effects from taking study medication. This research represents a greater than minimal risk to participants, but presents the prospect of direct benefit to individual subjects.

The research component of this study required to obtain 2 CT tumor biopsies confers radiation exposure at an effective dose of 0.29 rem. This dose is below NIH RSC guidelines of less than 5.0 rem per year in adults, and represents a slightly greater than minimal risk to patients. The imaging component of the study using ^{89}Zr-panitumumab PET/CT confers an effective dose up to 6.9 rem, and adds a radiation risk which is slightly greater than minimal risk to subjects and offers **no** direct benefit to individual subjects.

14.5 Patient Advocate

The patients' rights representative is available to patients receiving treatment on this protocol at the NIH Clinical Center at (301) 496-2626 in Building 10 of the Clinical Research Center, Room 1-3521, on the Bethesda NIH campus. Patients will be informed that they can contact the study PI or RN at any time with questions about their medical care, and that the patients' rights representative is also available to answer non-medical questions about the study.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: POTENTIAL DRUG INTERACTIONS

CYP3A4 Inhibitors

Acetaminophen	Cyclosporine	Glyburide	Modafinil	Ranolazine
Acetazolamide	Danazol	Grapefruit juice (2)	Nefazodone	Risperidone
Amiodarone	Dasatinib (1)	Haloperidol	Nelfinavir	Ritonavir
Amlodipine	Delavirdine	Hydralazine	Nevirapine	Saquinavir
Amprenavir	Desipramine	Ifosfamide	Nicardipine	Selegiline
Anastrozole	Dexmedetomidine	Imatinib	Nifedipine	Sertraline
Aprepitant	Diazepam	Indinavir	Nisoldipine	Sildenafil
Atazanavir	Diclofenac	Irbesartan	Nizatidine	Sirolimus
Atorvastatin	Dihydroergotamine	Isoniazid	Norfloxacin	Sulconazole
Azelastine	Diltiazem	Isradipine	Olanzapine	Tacrolimus
Azithromycin	Disulfiram	Itraconazole	Omeprazole	Tamoxifen
Betamethasone	Docetaxel	Ketoconazole	Orphenadrine	Telithromycin
Bortezomib	Doxorubicin	Lansoprazole	Oxybutynin	Teniposide
Bromocriptine	Doxycycline	Lidocaine	Paroxetine	Testosterone
Caffeine	Drospirenone	Lomustine	Pentamidine	Tetracycline
Cerivastatin	Efavirenz	Losartan	Pergolide	Ticlopidine
Chloramphenicol	Enoxacin	Lovastatin	Phencyclidine	Tranylcypromine
Chlorzoxazone	Entacapone	Mefloquine	Pilocarpine	Trazodone
Cimetidine	Ergotamine	Mestranol	Pimozide	Troleandomycin
Ciprofloxacin	Erythromycin	Methadone	Pravastatin	Valproic acid
Cisapride	Ethinyl estradiol	Methimazole	Prednisolone	Venlafaxine
Clarithromycin	Etoposide	Methoxsalen	Primaquine	Verapamil
Clemastine	Felodipine	Methylprednisolone	Progesterone	Vinblastine
Clofazimine	Fentanyl	Metronidazole	Propofol	Vincristine
Clotrimazole	Fluconazole	Miconazole	Propoxyphene	Vinorelbine
Clozapine	Fluoxetine	Midazolam	Quinidine	Voriconazole
Cocaine	Fluvastatin	Mifepristone	Quinine	Zafirlukast
Conivaptan	Fluvoxamine	Mirtazapine	Quinupristin	Ziprasidone
Cyclophosphamide	Fosamprenavir	Mitoxantrone	Rabeprazole	

CYP3A4 Inducers

Aminoglutethimide	Nafcillin	Pentobarbital	Primidone	Rifapentine
Carbamazepine	Nevirapine	Phenobarbital	Rifabutin	St. John's wort (3)
Fosphenytoin	Oxcarbazepine	Phenytoin	Rifampin	

CYP3A4 Substrates

Albuterol	Docetaxel	Ketoconazole	Quetiapine
Alfentanil	Doxepin	Lansoprazole	Quinidine
Alprazolam	Doxorubicin	Letrozole	Rabeprazole
Amlodipine	Doxycycline	Levomethadyl acetate hydrochloride	Repaglinide
Amprenavir	Efavirenz		Rifabutin
Aprepitant	Eletriptan	Levonorgestrel	Rifampin
Aripiprazole	Enalapril	Lidocaine	Ritonavir
Atazanavir	Eplerenone	Losartan	Saquinavir
Atorvastatin	Ergoloid mesylates	Lovastatin	Sertraline
Benzphetamine	Ergonovine	Medroxyprogesterone	Sibutramine
Bisoprolol	Ergotamine	Mefloquine	Sildenafil
Bortezomib	Erythromycin	Mestranol	Simvastatin
Bosentan	Escitalopram	Methadone	Sirolimus
Bromazepam	Estradiol	Methylergonovine	Sufentanil
Bromocriptine	Estrogens, conj., synthetic	Methysergide	Tacrolimus
Buprenorphine	Estrogens, conj., equine	Miconazole	Tamoxifen
Buspirone	Estrogens, conj., esterified	Midazolam	Tamsulosin

Busulfan	Estrone	Miglustat	Telithromycin
Carbamazapine	Estropipate	Mirtazapine	Teniposide
Cerivastatin	Ethinyl estradiol	Modafinil	Terbinafine
Chlordiazepoxide	Ethosuximide	Montelukast	Tetracycline
Chloroquine	Etoposide	Moricizine	Theophylline
Chlorpheniramine	Felbamate	Nateglinide	Tiagabine
Cisapride	Felodipine	Nefazodone	Ticlopidine
Citalopram	Fentanyl	Nelfinavir	Tolterodine
Clarithromycin	Flurazepam	Nevirapine	Toremifene
Clobazam	Flutamide	Nicardipine	Trazodone
Clonazepam	Fosamprenavir	Nifedipine	Triazolam
Clorazepate	Fulvestrant	Nimodipine	Trimethoprim
Cocaine	Gefitinib	Nisoldipine	Trimipramine
Colchicine	Halofantrine	Nitrendipine	Troleandomycin
Cyclophosphamide	Haloperidol	Norethindrone	Vardenafil
Cyclosporine	Ifosfamide	Norgestrel	Venlafaxine
Dantrolene	Imatinib	Ondansetron	Verapamil
Dapsone	Indinavir	Paclitaxel	Vinblastine
Delavirdine	Irinotecan	Pergolide	Vincristine
Diazepam	Isosorbide dinitrate	Phencyclidine	Vinorelbine
Digitoxin	Isosorbide mononitrate	Pimozide	Zolpidem
Dihydroergotamine	Isradipine	Pioglitazone	Zonisamide
Diltiazem	Itraconazole	Primaquine	Zopiclone
Disopyramide	Ketamine	Progesterone	

CYP2C19 INHIBITORS

Chloramphenicol	Indomethacin	Pantoprazole	
Cimetidine	Ketoconzaole	Probenicid	
Esomeprazole	Lansoprazole	Rabeprazole	
Felbamate	Modafinil	Ticlodipine	
Fluoxetine	Omeprazole	Topiramate	
Fluvoxamine	Oxcarbazepine		

CYP2C19 INDUCERS

Carbamazepine			
Norethindrone			
Prednisone			
Rifampicin			

CYP2C19 SUBSTRATES

Amitriptyline	Hexobarbital	Omeprazole	Teniposide
Carisoprodol	Imipramine	Pantoprazole	R-warfarin
Citalopram	Indomethacin	Phenobarbitone	
Chloramphenicol	Lansoprazole	Phenytoin	
Clomipramine	S-mephenytoin	Primidone	
Clopidogrel	R-mephobarbital	Progesterone	
Cyclophosphamide	Moclobemide	Proguanil	
N-DeME	Nelfinavir	Propanolol	
Diazepam	Nilutamide	Rabeprazole	

Because the lists of these agents are constantly changing, frequently-updated lists available at http://medicine.iupui.edu/clinpharm/ddis/table.asp will be consulted.

APPENDIX C: DRUGS WITH RISK OF TORSADES DE POINTES

Obtained from the Arizona Center for Education and Research on Therapeutics (AZCERT) website http://crediblemeds.org, last revised May 4, 2015.

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	oral, injection
Anagrelide	Agrylin®, Xagrid®	Phosphodiesterase 3 inhibitor	Thrombocythemia	Risk of TdP	oral
Arsenic trioxide	Trisenox®	Anti-cancer	Cancer (leukemia)	Risk of TdP	injection
Astemizole (Removed from US Market) (Removed from US Market)	Hismanal®	Antihistamine	Allergic rhinitis	Risk of TdP	oral
Azithromycin	Zithromax®, Zmax®	Antibiotic	Bacterial infection	Risk of TdP	oral, injection
Bepridil (Removed from US Market) (Removed from US Market)	Vascor®	Anti-anginal	Angina Pectoris (heart pain)	Risk of TdP	oral
Chloroquine	Aralen®	Anti-malarial	Malaria	Risk of TdP	oral
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Anti-psychotic / Anti-emetic	Schizophrenia, nausea, many others	Risk of TdP	oral, injection, suppository
Cilostazol	Pletal®	Phosphodiesterase 3 inhibitor	Intermittent claudication	Risk of TdP	oral
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	Antibiotic	Bacterial infection	Risk of TdP	oral, injection
Cisapride (Removed from US Market) (Removed from US Market)	Propulsid®	GI stimulant	Increase GI motility	Risk of TdP	oral
Citalopram	Celexa®, Cipramil®	Anti-depressant, SSRI	Depression	Risk of TdP	oral
Clarithromycin	Biaxin®, Prevpac®	Antibiotic	Bacterial infection	Risk of TdP	oral
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)	Risk of TdP	topical
Disopyramide	Norpace®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	oral
Dofetilide	Tikosyn®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	oral
Domperidone (On non US Market) (On non US Market)	Motilium®, Motillium®, Motinorm Costi®, Nomit®	Anti-nausea	Nausea, vomiting	Risk of TdP	oral, injection, suppository

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Donepezil	Aricept®	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)	Risk of TdP	oral
Dronedarone	Multaq®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	oral
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Anti-psychotic / Anti-emetic	Anesthesia (adjunct), nausea	Risk of TdP	injection
Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®	Antibiotic	Bacterial infection, increase GI motility	Risk of TdP	oral, injection
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E® (India), Exodus® (Brazil), Esto® (Israel), Seroplex®, Elicea®, Lexamil®, Lexam®, Entact® (Greece), Losita® (Bangladesh), Reposil® (Chile), Animaxen® (Colombia), Esitalo® (Australia), Lexamil® (South Africa)	Anti-depressant, SSRI	Depression (major), anxiety disorders	Risk of TdP	oral
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	oral
Fluconazole	Diflucan®, Trican®	Anti-fungal	Fungal infection	Risk of TdP	oral, injection
Grepafloxacin (Off market worldwide) (Off market worldwide)	Raxar®	Antibiotic	Bacterial infection	Risk of TdP	oral
Halofantrine	Halfan®	Anti-malarial	Malaria	Risk of TdP	oral
Haloperidol	Haldol® (US & UK), Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol® (Germany), Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®	Anti-psychotic	Schizophrenia, agitation	Risk of TdP	oral, injection
Ibutilide	Corvert®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	injection
Levofloxacin	Levaquin®, Tavanic®	Antibiotic	Bacterial infection	Risk of TdP	oral, injection

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Levomethadyl (Removed from US Market) (Removed from US Market)	Orlaam®	Opiate	Narcotic dependence	Risk of TdP	oral
Mesoridazine (Removed from US Market) (Removed from US Market)	Serentil®	Anti-psychotic	Schizophrenia	Risk of TdP	oral
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®	Opiate	Narcotic dependence, pain	Risk of TdP	oral, injection
Moxifloxacin	Avelox®, Avalox®, Avelon®	Antibiotic	Bacterial infection	Risk of TdP	oral, injection
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®	Anti-emetic	Nausea, vomiting	Risk of TdP	oral, injection
Pentamidine	Pentam®	Antifungal	Fungal infection (Pneumocystis pneumonia)	Risk of TdP	injection
Pimozide	Orap®	Anti-psychotic	Tourette's Disorder	Risk of TdP	oral
Probucol (Removed from US Market) (Removed from US Market)	Lorelco®	Antilipemic	Hypercholesterolemia	Risk of TdP	oral
Procainamide (Oral off US mkt) (Oral off US mkt)	Pronestyl®, Procan®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	injection
Propofol	Diprivan®, Propoven®	Anesthetic, general	Anesthesia	Risk of TdP	injection
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	oral, injection
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general	Anesthesia	Risk of TdP	inhaled
Sotalol	Betapace®, Sotalex®, Sotacor®	Anti-arrhythmic	Abnormal heart rhythm	Risk of TdP	oral
Sparfloxacin (Removed from US Market) (Removed from US Market)	Zagam®	Antibiotic	Bacterial infection	Risk of TdP	oral
Sulpiride (On non US Market) (On non US Market)	Dogmatil®, Dolmatil®, Eglonyl®, Espiride®, Modal®, Sulpor®	Anti-psychotic, atypical	Schizophrenia	Risk of TdP	oral
Terfenadine (Removed from US Market) (Removed from US Market)	Seldane®	Antihistamine	Allergic rhinitis	Risk of TdP	oral
Thioridazine	Mellaril®, Novoridazine®, Thioril®	Anti-psychotic	Schizophrenia	Risk of TdP	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Vandetanib	Caprelsa®	Anti-cancer	Cancer (thyroid)	Risk of TdP	oral

Next page:

APPENDIX D: ^{89}Zr-LABELED PANITUMUMAB ORDER FORM

^{89}Zr-panitumumab Order Form		
Site	**Subject / Patient ID**	**Date of Request *** DD MM YYYY
Scheduled ^{89}Zr-Panitumumab Scan DD MM YYYY	**Time** *24 hr clock*	**Dose Activity** mCi

1. Site Section : Complete and fax to Leidos Radiopharmacy at 301-228-4624

*Please place ^{89}Zr-Panitumumab orders 5 business days prior to scheduled scan date and time.

Site Contact Information	
Site Name:	
Principal Investigator:	
Study Coordinator:	
NCI Protocol Number:	
Shipping Information	
Account Name:	
Contact Name:	
Contact Phone & Email or Fax:	
Shipment Address:	

2. Leidos Radiopharmacy Section: Confirm receipt of Request Form and fax or e-mail to Clinical Site

^{89}Zr-Panitumumab Request Form received on ___ ___ _____ by _____
DD MM YYYY Print Name

3. Leidos Radiopharmacy Section

Date request received:	*Leidos Radiopharmacy Shipment Number:*
Tracking Number:	*Mode of Transportation:*
Batch Number:	*Attachments:*

Please affix copy of the syringe label below

Checked by:	*Packed by:*	*Date Shipped:*

APPENDIX E - PATIENT STUDY CALENDAR

The study drugs are given over a 28-day period of time called cycles. The 28-day treatment cycle will be repeated as long as you are tolerating the medications and your cancer is either stable or getting better.
The chart below shows what will happen to you during cycle 1 and future cycles after you sign the consent form and start the study. Each cycle is numbered. The left-hand column shows the day in the cycle, and the right-hand column tells you what will happen on that day.

Day	What to do and what will happen to you
Before starting study drug	• Check in at the Outpatient Clinic • Get routine blood tests and electrocardiogram of your heart (EKG) • Urine tests to check for protein in your urine • Pregnancy test for women who are able to become pregnant • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • CT or MRI scan will be done • Echocardiogram or MUGA scan will be done to check your heart • Eye exam • Blood draws for research will be obtained from some patients • For patients who agree to undergo ^{89}Zr-panitumumab PET/CT, baseline scans will be done prior to the start of cycle 1.
Cycle 1, Day 1	• Get routine blood tests and EKG (does not need to be repeated if done within 3 days before starting treatment) • Urine tests to check for protein in your urine (does not need to be repeated if done within 3 days before starting treatment) • Receive the first dose of ziv-aflibercept through a vein • Receive the first dose of ganetespib through a vein; for patients who have tumor biopsies, this dose of ganetespib will not be given
Cycle 1, Day 2	• An electrocardiogram of your heart will be done approximately 24 hours after receiving ganetespib
Cycle 1, Day 7	• For patients who have agreed to undergo tumor biopsies, the first tumor biopsy will take place on this day
Cycle 1, Day 8	• Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • Blood draws for research will be obtained from some patients. Get routine blood tests and EKG • Ganetespib will be given through a vein

Day	What to do and what will happen to you
Cycle 1, Day 9	• An electrocardiogram of your heart will be done approximately 24 hours after receiving ganetespib
Cycle 1, Day 15	• Check in at the Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • Get routine blood tests and EKG • Urine tests to check for protein in your urine • Ziv-aflibercept will be given through a vein • Ganetespib will be given through a vein • Blood draws for research will be obtained from some patients
Cycle 1, Day 16	• An electrocardiogram of your heart will be done approximately 24 hours after receiving ganetespib • For patients who agree to undergo ^{89}Zr-panitumumab PET/CT, post-treatment scans will be done on this day. If there are scheduling conflicts, scans may be done during Cycle 2, Day 16.
Cycle 1, Day 22	• No drug is given
Cycle 2, Day 1	• Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • Get routine blood tests and EKG • Urine tests to check for protein in your urine • Ziv-aflibercept will be given through a vein • Ganetespib will be given through a vein
Cycle 2, Day 7	• For patients who having tumor biopsies, the second tumor biopsy will take place on this day prior to treatment with ganetespib.
Cycle 2, Day 8	• Check in at the Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • Blood draws for research will be obtained from some patients • Get routine blood tests and EKG • Ganetespib will be given through a vein
Cycle 2, Day 15	• Check in at the Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • Get routine blood tests and EKG • Urine tests to check for protein in your urine

Day	What to do and what will happen to you
	• Ziv-aflibercept will be given through a vein • Ganetespib will be given through a vein • Blood draws for research will be obtained from some patients
Cycle 2, Day 16	• For patients who agree to undergo ^{89}Zr-panitumumab PET/CT, post-treatment scans not performed during cycle 1, day 16 can have scans rescheduled to this day.
Cycle 2, Day 22	• No drug is given
Cycle 3, Day 1 and 15, and onward	• Check in at the Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • Get routine blood tests and EKG • Urine tests to check for protein in your urine • CT scan to determine how your tumor is responding to the treatment will be done every 8 weeks (every 2 cycles) • Ziv-aflibercept will be given through a vein • Ganetespib will be given through a vein • Blood draws for research will be obtained from some patients on day 1 of every cycle
Cycle 3, Day 8, and onward	• Check in at the Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • Get routine blood tests and EKG • Ganetespib will be given through a vein

APPENDIX F: EXPANSION PHASE PD COLLECTION WORKSHEETS

Date:	**PD BLOOD SAMPLE COLLECTION SHEET: CYCLE 1 DAY 1**	
CTEP Protocol P9605 **Dose level:** **Patient ID:**	**Page 102-12798 for Sample Pick-up** **Lab phone: 301-451-1169**	**Research Nurse:** Phone: **Lead AI/PI:** Phone:

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Day 1	**Prior to drug administration**	**PD 400** 2x 4 mL K3 EDTA Label tube: sample number, date and time			

Date:	**PD BLOOD SAMPLE COLLECTION SHEET: CYCLE 1 DAY 8**	
CTEP Protocol P9605 **Dose level:** **Patient ID:**	**Page 102-12798 for Sample Pick-up** **Lab phone: 301-451-1169**	**Research Nurse:** Phone: **Lead AI/PI:** Phone:

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Day 8	**Prior to drug administration***	**PD 401** 2x 4 mL K3 EDTA Label tube: sample number, date and time			

**No drugs administered on Day 7; Ganetespib administered on Day 8*

Date:	PD BLOOD SAMPLE COLLECTION SHEET: CYCLE 1 DAY 15				
CTEP Protocol P9605 **Dose level:** **Patient ID:**		**Page 102-12798 for Sample Pick-up** **Lab phone: 301-451-1169**			**Research Nurse:** Phone: **Lead AI/PI:** Phone:
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
Day 15	**Completion time of Ziv-aflibercept and Ganetespib IV administration:**				
Day 15	**4 hr after completion of drug administration**	**PD 402** 2x 4 mL K3 EDTA Label tube: sample number, date and time			

Date:	PD BLOOD SAMPLE COLLECTION SHEET: CYCLE 2 DAY 8				
CTEP Protocol P9605 **Dose level:** **Patient ID:**		**Page 102-12798 for Sample Pick-up** **Lab phone: 301-451-1169**			**Research Nurse:** Phone: **Lead AI/PI:** Phone:
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
Day 8	**Prior to drug administration***	**PD 403** 2x 4 mL K3 EDTA Label tube: sample number, date and time			

**No drugs administered on Day 7; Ganetespib administered on Day 8*

Date:	**PD BLOOD SAMPLE COLLECTION SHEET: CYCLE 2 DAY 15**				
CTEP Protocol P9605 **Dose level:** **Patient ID:**		**Page 102-12798 for Sample Pick-up** **Lab phone: 301-451-1169**			**Research Nurse:** Phone: **Lead AI/PI:** Phone:
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
Day 15	**Completion time of Ziv-aflibercept and Ganetespib IV administration:**				
Day 15	**4 hr after completion of drug administration**	**PD 404** 2x 4 mL K3 EDTA Label tube: sample number, date and time			

Date:	**PD BLOOD SAMPLE COLLECTION SHEET: DAY 1 EACH CYCLE/PER PI**				
CTEP Protocol P9605 **Dose level:** **Patient ID:**		**Page 102-12798 for Sample Pick-up** **Lab phone: 301-451-1169**			**Research Nurse:** Phone: **Lead AI/PI:** Phone:
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
Day	**Before drug administration**	**PD 40X** 2x 4 mL K3 EDTA Label tube: sample number, date and time			