Phase 1B/2 Study of PAC-1 and Entrectinib for Patients with Metastatic Uveal Melanoma

Sponsor-Investigator
Arkadiusz Z. Dudek, MD, PhD
HealthPartners and Regions Cancer Care Centers
St. Paul, Minnesota

Principal Investigator
Yan Ji, MD
HealthPartners Regions Cancer Care and
Frauenshuh Cancer Care Centers
Suite 1161 Mail Stop 11101G
640 Jackson Street, St. Paul, MN 55101
Tel: 651 254-3321
Fax: 651 254-3102

Co-Investigator
Bryan Trottier, MD
HealthPartners Regions Cancer Care and
Frauenshuh Cancer Care Centers
Suite 1161 Mail Stop 11101G
640 Jackson Street, St. Paul, MN 55101
Tel: 651 254-3321
Fax: 651 254-3102

Statistician
Lauren Erickson, PhD
HealthPartners Institute
Bloomington, Minnesota

Trial Management Provided by
Hoosier Cancer Research Network, Inc.
500 N. Meridian, Suite 100
Indianapolis, IN 46204

Trial Supported by
Vanquish Oncology, Inc.
Genentech

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PROTOCOL SIGNATURE PAGE

Phase 1B/2 Study of PAC-1 and Entrectinib for Patients with Metastatic Uveal Melanoma

VERSION DATE: 04DEC2020

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable institutional review board(s).

_____ _____
Signature of Site Investigator Date

_____
Site Investigator Name (printed)

_____
Site Investigator Title

_____
Name of Facility

_____
Location of Facility (City and State)

PLEASE COMPLETE AND EMAIL A COPY TO HCRN

SYNOPSIS

TITLE	Phase 1B/2 Study of PAC-1 and Entrectinib for Patients with Metastatic Uveal Melanoma
SHORT TITLE	PAC-1 and Entrectinib for Patients with Metastatic Uveal Melanoma
PHASE	1B/2
OBJECTIVES	**Primary Objectives** **Phase 1b:** The primary objective of this study component is to determine the maximum tolerated dose (MTD) of PAC-1 in combination with entrectinib in subjects with metastatic uveal melanoma, by evaluation of toxicity and tolerability. **Phase 2:** The primary objective of this study component is to measure 3 months progression-free survival (PFS) rate, using RECIST v1.1, in subjects with metastatic uveal melanoma treated with entrectinib and PAC-1. **Secondary Objectives** **Phase 1b:** Evaluate the safety of entrectinib and PAC-1 combination, assessed by the incidence and severity of drug-related adverse events (AE), in subjects with metastatic uveal melanoma. **Phase 2** • Evaluate the safety of entrectinib and PAC-1 combination, assessed by the incidence and severity of drug-related AEs, in subjects with metastatic uveal melanoma. • Estimate the ORR in subjects with metastatic uveal melanoma treated with entrectinib and PAC-1. • Estimate DoR in subjects with metastatic uveal melanoma. • Estimate OS rate in subjects with metastatic uveal melanoma treated with entrectinib and PAC-1. **Correlative/Exploratory Objectives** • Determine pharmacokinetics/pharmacodynamics of PAC-1 alone after single dosing and after repeated dosing and in combination with entrectinib (Phase 1b only). • Determine pharmacokinetics/pharmacodynamics of entrectinib alone after single dosing and after repeated dosing and in combination with PAC-1 (Phase 1b only). • Compare procaspase 3 expression in tumor tissue to degree of clinical response. • Determine correlation between CTC number and clinical response.

STUDY DESIGN	Single arm study with dose escalation Phase Ib cohort followed by a Phase II cohort. PAC-1 (PO) will be given daily on Days 1 through 21 of each cycle (28-day cycle). Entrectinib (PO) will be given daily on Days 1 through 28 of each cycle. Response will be evaluated after every 2 cycles. Treatment will continue until disease progression based on RECIST criteria or intolerable toxicity.
ELIGIBILITY CRITERIA (See Section 3 for complete list of eligibility criteria)	**Inclusion Criteria** 1. Histologically or cytologically confirmed metastatic uveal melanoma. 2. One or more lesions that could be accurately measured using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. 3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. 4. Adequate organ function within 14 days of registration. 5. Subjects must have archival tissue (metastatic disease preferred) available or agree to undergo a biopsy prior to C1D1 treatment. 6. Prior therapy is allowed but must have been completed 21 days prior to initiation of protocol therapy and all toxicities must be < Grade 2. 7. Palliative radiation must have been completed 2 weeks prior to the initiation of study therapy. 8. Patient with known brain metastases must have been treated at least 2 weeks prior to enrollment, be asymptomatic from brain metastases, stable on brain imaging, and not be receiving a supra-physiologic dose of steroids (>10 mg prednisone daily or equivalent). 9. All females of childbearing potential must have a urine HCG test or blood HCG test within 2 weeks prior to registration to rule out pregnancy. **Exclusion Criteria** 1. Peripheral sensory neuropathy Grade ≥ 2 (per CTCAE v5.0). 2. Active gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes that would reasonably impact drug absorption. 3. Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies). 4. Has known active Hepatitis B or C. Active Hepatitis B is defined as a known positive HBsAg result. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay. For patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg), the patient is only eligible if they are negative for HBV DNA. 5. Known interstitial lung disease, interstitial fibrosis, or history of tyrosine kinase inhibitor-induced pneumonitis. **NOTE:** Radiation-induced lung disorders are not included in this exclusion criterion.

	6. History of retinal pigmented epithelial detachment, central serous retinopathy, or retinal vein occlusion in the unaffected eye; or intraocular pressure 21 mmHg or uncontrolled glaucoma (irrespective of intraocular pressure) in the unaffected eye 7. History of uncontrolled seizures 8. History of ataxia 9. Allergies and adverse drug reaction: History of allergy to study drug components 10. Thromboembolic events requiring therapeutic anticoagulation. Concomitant anticoagulation with oral anticoagulants (warfarin, direct thrombin or factor Xa inhibitors), platelet inhibitors (eg. Clopidogrel, high dose aspirin) is prohibited. Low-dose aspirin (≤100 mg/day), low-dose warfarin (≤1 mg/day) and prophylactic low molecular weight heparin (LMWH) or similar agents are permitted. 11. History of recent (within the past 3 months) symptomatic congestive heart failure or ejection fraction ≤50% observed during screening for the study. 12. History of prolonged QTc interval (e.g., repeated demonstration of a QTc interval > 450 milliseconds from ECGs performed at least 24 hours apart). 13. History of additional risk factors for torsades de pointes (e.g., family history of long QT syndrome). 14. Cardiovascular disorders including unstable angina pectoris, clinically-significant cardiac arrhythmias, myocardial infarction or stroke (including transient ischemic attack [TIA], or other ischemic event) within 6 months prior to registration. 15. Active infection requiring intravenous systemic treatment. 16. Serious non-healing wound/ulcer/bone fracture within 28 days prior to registration. 17. Known uncontrolled, symptomatic brain metastasis or cranial epidural disease. 18. Known additional malignancies which require systemic treatment. 19. Inability to swallow intact tablets.

STATISTICAL CONSIDERATIONS	**Phase 2** The primary endpoint of the study is 3 month progression-free survival (PFS) rate, using RECIST v1.1, in subjects with metastatic uveal melanoma treated with entrectinib and PAC-1. Kaplan Meier curve will be used to evaluate PFS, and OS; descriptive statistics for response rate, DoR, and toxicity. **Sample Size** Previous studies in the target population identified PFS at 3 months of 38%.[6] We hypothesize PFS at 3 months of 65%. Controlling for a probability of Type I error at 0.05 (one-sided), our sample size in Phase 2 is estimated to be 32 to ensure 90% statistical power in successfully detecting an alternative progression free survival rate at 3 months of 0.65, compared to a null rate of 0.38. With 3 additional patients to account for a 10% drop off rate, sample size for phase 2 study will be 35. Sample size analyses were conducted using the PASS software (NCSS, Kaysville, Utah, USA). With Phase 1b study component, the study will need to have 3 subjects from Dose Level 1 of Phase 1b + 6 subjects from Dose Level 2 of Phase 1b (and carried over to Phase 2 study).
TOTAL NUMBER OF SUBJECTS	Total number of subjects for the study is 38
ESTIMATED ENROLLMENT PERIOD	Estimated 18 months
ESTIMATED STUDY DURATION	Estimated 24 months

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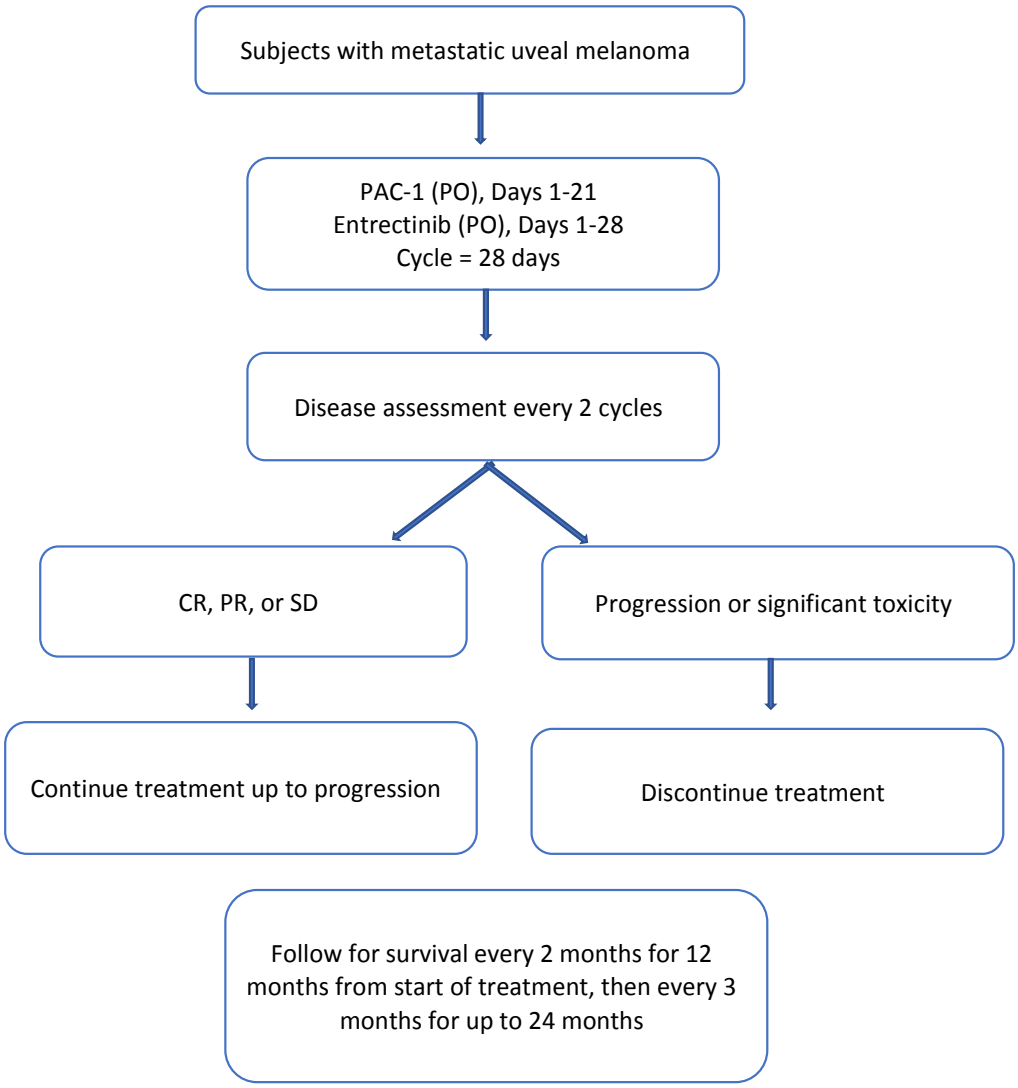
PHASE 1b SCHEMA

The primary objective of the Phase Ib study is to establish the maximum tolerated dose (MTD) of PAC-1 in combination with entrectinib for subjects with metastatic uveal melanoma, by evaluation of toxicity and tolerability.

Phase 1b



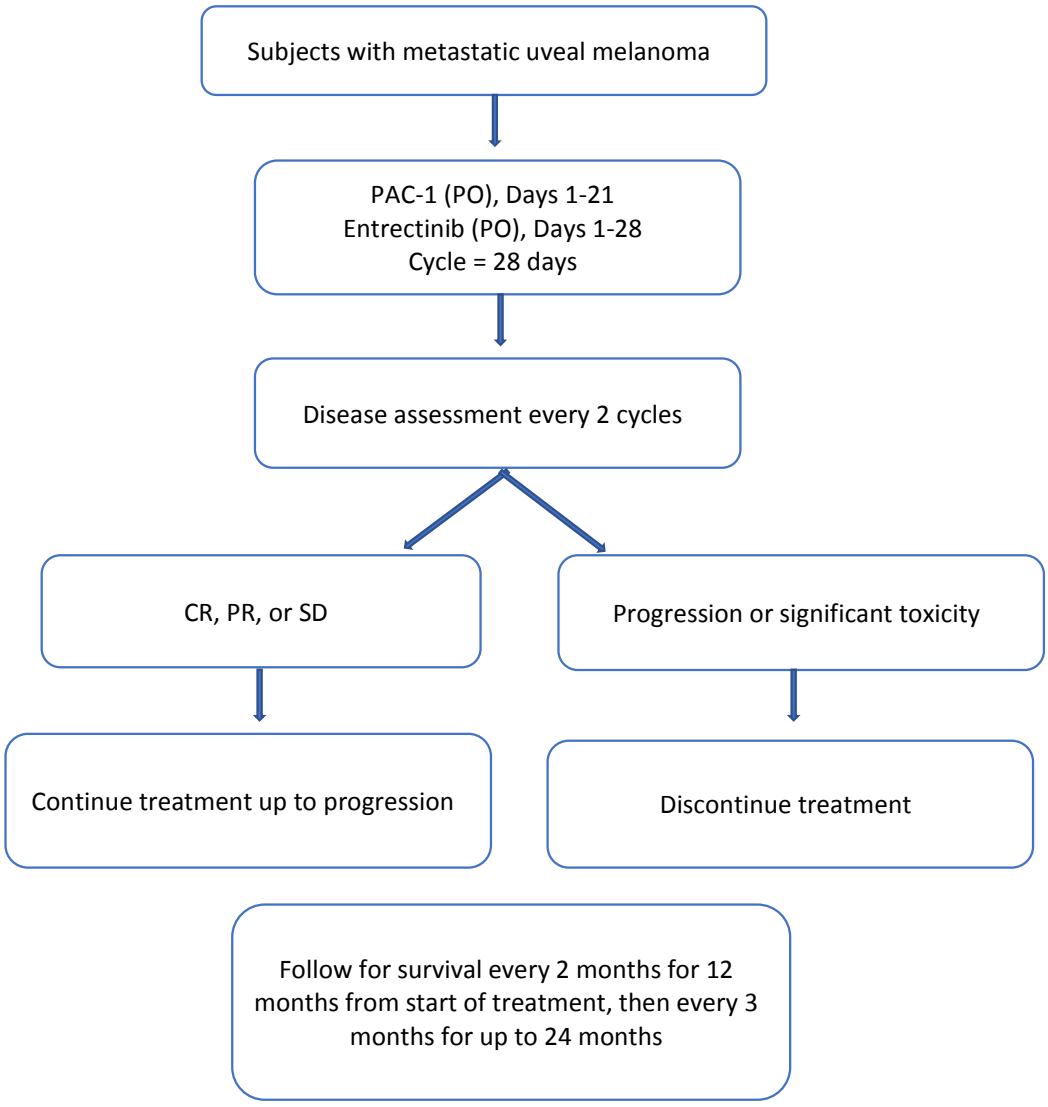
Dose Level*	PAC-1 Dose (mg, orally)	Entrectinib (mg, orally)	# of Subjects#
-1	625 daily	400 daily	3-6
1	625 daily	600 daily	3-6
2	750 daily	600 daily	3-6

#MTD cohort will be initially expanded to 6 patients, and if no DLT, to Phase 2 study.

PHASE 2 SCHEMA

The primary objective of the Phase 2 Study is to estimate 3 month progression-free survival (PFS) using RECIST v1.1 in subjects with metastatic uveal melanoma.

Phase II



Entrectinib dosed at 600 mg once daily; PAC-1 dosed once daily at RP2D from Phase 1b study.

ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ANC	absolute neutrophil count
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood count
cm	centimeter
CMP	comprehensive metabolic panel
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CYP	cytochrome P450
dL	deciliter
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ERK	extracellular signal-regulated kinase
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
GFR	glomerular filtration rate
h	hour
Hgb	hemoglobin
IB	Investigator's Brochure
IND	Investigational New Drug
IRB	institutional review board
kg	kilogram
lbs	pounds
LDH	lactic dehydrogenase
mg	milligram
min	minute
mL	milliliter
mm^3	cubic millimeters

MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine kinase
ORR	overall response rate
OS	overall survival
PAC-1	first procaspase-activating compound
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
RECIST	Response Evaluation Criteria in Solid Tumor
ROS1	ROS proto-oncogene 1
SAE	serious adverse event
SDEA	Safety Data Exchange Agreement
TKI	tyrosine kinase inhibitor
Trk	tropomyosin-related kinase
ULN	upper limit of normal
US	United States
WHO	World Health Organization
WOCP	women of childbearing potential
wt	weight

1. BACKGROUND AND RATIONALE

1.1 Uveal Melanoma

Uveal melanoma arises from the uveal tract of the eye, which includes the choroid, ciliary body, and iris, and is the most common primary intraocular malignancy in adults.[1] Uveal melanoma is biologically different from cutaneous melanoma[2] and accounts for approximately 3% to 5% of all melanoma. There are currently no approved or effective systemic treatment options for individuals with metastatic uveal melanoma. Mutations in GNAQ or GNA11 are found in more than 80% of uveal melanomas, resulting in constitutive activation of the RAS/RAF/MEK/ERK pathway.[3-5]

1.2 Current Treatment of Uveal Melanoma

There are more than 40 clinical trials reported in uveal melanoma with average response rate of 4%. Current standard of care is dacarbazine. In a recent randomized clinical SUMMIT trial of selumetinib in combination with dacarbazine in patients with metastatic uveal melanoma the objective response rate (ORR) was 3%, with progression-free survival (PFS) of 2.8 months in selumetinib plus dacarbazine treatment group. Three- and 6-month PFS rates were 38% and 10%, respectively.[6] Overall survival (OS) was only 10 months.

1.3 Entrectinib

Entrectinib is a potent tyrosine kinase inhibitor (TKI) that targets the product of oncogenic rearrangements in neurotrophic tyrosine kinase (NTRK), ROS proto-oncogene 1 (ROS1), and anaplastic lymphoma kinase (ALK). Two phase I trials demonstrated activity in TKI-naïve patients along with substantial intracranial activity. In ROS1-rearranged lung cancers, entrectinib resulted in durable disease control and prolonged PFS. The drug was well tolerated and has a safety profile that includes adverse events mediated by on-target tropomyosin-related kinase (Trk) A/B/C inhibition. Refer to the current investigator's brochure for details regarding adverse events related to entrectinib.

1.4 First Procaspase-Activating Compound

Members of the caspase family of cysteine proteases are key players in both the initiation and execution of apoptosis.[8] Most critical to apoptosis is the proteolytic conversion of procaspase-3 to caspase-3. As both the intrinsic and extrinsic apoptotic pathways converge to activate procaspase-3, and as caspase-3 has over 100 cellular substrates, the activation of procaspase-3 to caspase-3 is a pivotal and committed event in the apoptotic cascade.[9] Procaspase-3 levels are elevated in a variety of tumors including glioblastoma[10], breast cancer[11] , colon cancer[12], lung cancer[13], lymphoma[14], neuroblastoma[15], melanoma[16], and liver cancer[17]. First procaspase-activating compound (PAC-1) is a small molecule, which enhances procaspase-3 activity *in vitro*[18], induces apoptotic death of cancer cells in culture[9,18,19], and has efficacy in multiple mouse xenograft models[18,20]. There is a strong correlation between cellular procaspase-3 levels and the apoptosis-inducing properties of PAC-1.[18] PAC-1 has shown toxicity in mice, rats and dogs. The toxicity is more typically observed with high doses. However, in one study testing relatively lower doses of PAC-1 given orally daily for 28 days in dogs, there was evidence of minimal-mild neurodegeneration (unpublished study). Overall, PAC-1 has several attributes which makes this a potentially efficacious anticancer drug in humans. Accordingly, we are presently conducting a study consisting of two components: to determine the maximum tolerated

dose (MTD) of PAC-1 in solid tumor or hematologic malignancy (NCT02355535), and to determine the maximum tolerated dose of PAC-1 when combined with the front-line chemotherapeutic agent, temozolomide, in patients with primary brain tumors (NCT03332355). Primary endpoints are evaluation of tolerability and toxicity. Neurological symptoms of CNS toxicity are being assessed throughout the trial.

PAC-1 has been dosed in 44 human patients through 7 dose levels of PAC-1 (range: 75-750 mg). Two patients progressed during the first cycle of PAC-1 therapy. Thirty-two patients received PAC-1 for at least 2 dosing cycles (a cycle is 21 days of daily dosing followed by 7 days of no drug). As a result of stable disease responses, six patients received PAC-1 for 4 cycles, three patients received PAC-1 for 6 cycles and two patients received PAC-1 for 10 cycles. No serious adverse events (SAEs) associated with PAC-1 administration have been observed. Further, after careful review of all neurological and neurocognitive assessments and data collected through dose level 7 (750 mg) there were no signs of neurotoxicity associated with PAC-1 dosing. In this study, physicians will utilize the MOCA-Montreal Cognitive Assessment Test Form for subject assessment at screening and Day 1 of each Cycle.

1.5 Rationale

We have performed an *in vitro* study of PAC-1 and entrectinib combination in seven uveal melanoma cell lines (GNAQ mutant; MEL270, 92.1, MEL202, OMM2.5, GNA11 mutant: OMM1, and GNAQ and GNA11 wild type: MEL285, and MEL290). In all seven cell lines we saw a synergistic killing effect of PAC-1 and entrectinib (data unpublished). We propose that entrectinib will synergize with PAC-1 in human patients with metastatic melanoma and will produce superior prolongation of PFS.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives

2.1.1 Phase 1b

The primary objective of this study component is to determine the maximum tolerated dose (MTD) of PAC-1 in combination with entrectinib in patients with metastatic uveal melanoma, by evaluation of toxicity and tolerability.

2.1.2 Phase 2

The primary objective of this study component is to measure 3 months progression-free survival (PFS) rate in subjects with metastatic uveal melanoma treated with entrectinib and PAC-1.

2.2 Secondary Objectives

2.2.1 Phase 1b

Evaluate the safety of entrectinib and PAC-1 combination, assessed by the incidence and severity of drug-related adverse events (AE), in subjects with metastatic uveal melanoma.

2.2.2 Phase 2

- Evaluate the safety of entrectinib and PAC-1 combination, assessed by the incidence and severity of drug-related adverse events (AE), in subjects with metastatic uveal melanoma.
- Estimate the ORR in subjects with metastatic uveal melanoma treated with entrectinib and PAC-1.
- Estimate DoR in subjects with metastatic uveal melanoma.
- Estimate OS rate in subjects with metastatic uveal melanoma treated with entrectinib and PAC-1.

2.3 Correlative/Exploratory Objectives

- Determine pharmacokinetics (PK)/pharmacodynamics (PD) of PAC-1 alone after single dosing and after repeated dosing and in combination with entrectinib (Phase 1b only).
- Determine pharmacokinetics/pharmacodynamics of entrectinib alone after single dosing and after repeated dosing and in combination with PAC-1 (Phase 1b only).
- Compare procaspase 3 expression in tumor tissue to degree of clinical response
- Determine correlation between CTC number and clinical response.

2.4 Primary Endpoints

2.4.1 Phase 1b

- The MTD of PAC-1 in combination with entrectinib is the highest tested dose of PAC-1 combined with entrectinib with DLT rate of less than 33% in first cycle of therapy (i.e., ≤1 out of 6 subjects with DLT).

2.4.2 Phase 2

- PFS at 3 months; this is defined as proportion of alive subjects with metastatic uveal melanoma at 3 months from treatment initiation with PAC-1 in combination with entrectinib without evidence of radiological disease progression by RECIST 1.1.

2.5 Secondary Endpoints

2.5.1 Phase 1b

Safety and tolerability by NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5 on treatment with PAC-1 in combination with entrectinib in subjects with metastatic uveal melanoma.

2.5.2 Phase 2

- Safety and tolerability by NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5 on treatment with PAC-1 in combination with entrectinib in subjects with metastatic uveal melanoma.
- ORR; which will include CR + PR determined as per RECIST1.1 on treatment with PAC-1 in combination with entrectinib in subjects with metastatic uveal melanoma.
- DoR on treatment with PAC-1 in combination with entrectinib in subjects with metastatic uveal melanoma. DoR is defined as the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that

recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).
- OS; this is defined as the time from treatment initiation with PAC-1 in combination with entrectinib until death as a result of any cause in subjects with metastatic uveal melanoma.

2.6 Correlative/Exploratory Endpoints
- PK endpoints of PAC-1 include plasma concentration-time curve from time 0 to 24 hours (AUC_{0-24}) for days 1 and 21 (see section on Pharmacokinetic Analysis for other endpoints) (Phase 1b only).
- PK endpoints of entrectinib include plasma concentration-time curve from time 0 to 24 hours (AUC_{0-24}) for days 3 and 21 (see section on Pharmacokinetic Analysis for other endpoints) (Phase 1b only).
- Compare procaspase 3 expression in tumor tissue to degree of clinical response.
- Determine correlation between CTC number and clinical response.

3 ELIGIBILITY REQUIREMENTS

3.1 Inclusion Criteria
Study entry is open to adults regardless of gender or ethnic background. While there will be every effort to seek out and include men and minorities, the subject population is expected to be no different than that of other advanced solid tumor cancer studies at each participating institution.

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information prior to registration. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately. Patients must be willing and able to provide written informed consent for this trial.

2. Age ≥ 18 years at the time of consent.

3. Histologically or cytologically confirmed metastatic uveal melanoma. Staging per AJCC manual edition 8.

4. One or more lesions that could be accurately measured using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (Appendix 1).

6. Subjects must have archival tissue (metastatic disease preferred) available or undergo a biopsy prior to Cycle 1 Day 1 of treatment. Subjects that do not have archival tissue or cannot undergo a biopsy are not eligible for the study.

7. Demonstrate adequate organ function as defined in the table below. All screening labs to be obtained within 14 days prior to registration.

System	Laboratory Value
Hematological	
Leukocytes	≥ 2,000 μ/l
Absolute Neutrophil Count (ANC)	≥ 1,500 K/mm^3
Platelets	≥ 100,000/ mm^3
Hemoglobin (Hgb)	≥ 9 g/dL
Renal	
Serum Creatinine	≤ 1.5 x ULN
Calculated creatinine clearance[1]	≥ 40 mL/min
Hepatic	
Total Bilirubin	≤ 1.5 mg/dL; (except for subjects with Gilbert Syndrome, who can have total bilirubin <3.0 mg/dl)
Aspartate aminotransferase (AST)	≤ 2.5 × ULN
Alanine aminotransferase (ALT)	≤ 2.5 × ULN
Alkaline Phosphatase	≤ 2.5 × ULN; (<5 x ULN if liver metastases present)
Coagulation	
Partial Thromboplastin Time (PTT)	< 1.5 × ULN

[1] Cockcroft-Gault formula will be used to calculate creatinine clearance

8. Prior therapy is allowed but must have been completed 21 days prior to initiation of protocol therapy and all toxicities must be < Grade 2.

9. Palliative radiation must have been completed 2 weeks prior to the initiation of study therapy.

10. Patient with known brain metastases must have been treated at least 2 weeks prior to enrollment, be asymptomatic from brain metastases, stable on brain imaging, and not be receiving a supra-physiologic dose of steroids (>10 mg prednisone daily or equivalent).

11. Women must not be pregnant or breastfeeding. All women of childbearing potential (WOCBP) must have a blood human chorionic gonadotrophin (hCG) test or urine hCG test within 2 weeks prior to registration to rule out pregnancy.

12. Women of childbearing potential (WOCBP) must agree to use contraception as outlined in Section 5.8 from the time of informed consent, during the study and for 3 months after the last dose of study drug(s). Abstinence from heterosexual intercourse is an acceptable form of contraception. Women of childbearing potential are those who have not been surgically sterilized or have not been free of menses >1 year.

13. Male patients who are sexually active with WOCBP must agree to use contraception as outlined in Section 5.8 from the time of initiation of study treatment, during the study and for 3 months after the last dose of study drug(s). Abstinence from heterosexual intercourse is an acceptable form of contraception.

14. The participant is capable of understanding and complying with the protocol and has signed informed consent document.

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Peripheral sensory neuropathy Grade ≥ 2 (per CTCAE v5.0).

2. Active gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes that would reasonably impact drug absorption.

3. Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

4. Has known active Hepatitis B or C. Active Hepatitis B is defined as a known positive HBsAg result. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay. For patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg), the patient is only eligible if they are negative for HBV DNA.

5. Known interstitial lung disease, interstitial fibrosis, or history of tyrosine kinase inhibitor-induced pneumonitis. **NOTE:** Radiation-induced lung disorders are not included in this exclusion criterion.

6. History of retinal pigmented epithelial detachment, central serous retinopathy, or retinal vein occlusion in the unaffected eye; or intraocular pressure 21 mmHg or uncontrolled glaucoma (irrespective of intraocular pressure) in the unaffected eye.

7. History of uncontrolled seizures.

8. History of ataxia.

9. Allergies and adverse drug reaction: History of allergy to study drug components.

10. Thromboembolic events requiring therapeutic anticoagulation. Concomitant anticoagulation with oral anticoagulants (warfarin, direct thrombin or factor Xa inhibitors), platelet inhibitors (e.g. Clopidogrel, high dose aspirin) is prohibited. Low-dose aspirin (≤100 mg/day), low-dose warfarin (≤1 mg/day) and prophylactic low molecular weight heparin (LMWH) or similar agent are permitted.

11. History of recent (within the past 3 months) symptomatic congestive heart failure or ejection fraction ≤50% observed during screening for the study.

12. History of prolonged QTc interval (e.g., repeated demonstration of a QTc interval > 450 milliseconds from ECGs performed at least 24 hours apart).

13. History of additional risk factors for torsades de pointes (e.g., family history of long QT syndrome).

14. Cardiovascular disorders including unstable angina pectoris, clinically-significant cardiac arrhythmias, myocardial infarction or stroke (including transient ischemic attack [TIA], or other ischemic event) within 6 months prior to registration.

15. Active infection requiring intravenous systemic treatment.

16. Serious non-healing wound/ulcer/bone fracture within 28 days prior to registration.

17. Known uncontrolled, symptomatic brain metastasis or cranial epidural disease.

18. Known additional malignancies which require systemic treatment.

19. Inability to swallow intact tablets.

20. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study or could compromise protocol objectives in the opinion of the Investigator and/or the sponsor-investigator.

4 SUBJECT REGISTRATION

All subjects must be registered through HCRN's electronic data capture (EDC) system. A subject is considered registered when an "On Study" date is entered into the EDC system. Subjects must be registered prior to starting protocol therapy. Subjects must begin therapy **within 7 business days** of registration.

5 OVERALL DESIGN AND TREATMENT PLAN

5.1 Phase 1b Dose Escalation Plan

This Phase Ib dose escalation study will evaluate entrectinib in combination with PAC-1 in subjects with metastatic uveal melanoma. Entrectinib will be taken orally on Days 1-28 of each 28 day cycle and PAC-1 will be taken orally on Days 1-21 of each 28-day cycle (see exception for Cycle 1 below), and response to treatment will be evaluated after every 2 cycles. Treatment will continue until disease progression (based on RECIST 1.1 criteria), unacceptable toxicity, subject withdrawal of informed consent, or subject death either from progression of disease, the therapy itself, or from other causes. Subjects who withdrew from study treatment, have progressive disease, or unacceptable toxicities will be followed for survival every 2 months for 12 months from start of study treatment, then every 3 months for up to 24 months.

Pharmacokinetic (PK) and pharmacodynamic (PD) assay for PAC-1 will be performed during Days 1 and 21 of Cycle 1. PAC-1 will be given on Day 1 of Cycle 1, withheld on Day 2 and Day 3 of Cycle 1 then reinitiated on Day 4 of Cycle 1 to continue to Day 21 of the 28-day cycle. For

each successive cycle, PAC-1 therapy will be initiated on Day 1 and continue to Day 21 of the 28-day cycle.

Pharmacokinetic and pharmacodynamic assay for entrectinib will be performed during Days 3 and 21 of Cycle 1. Entrectinib therapy will be withheld on Day 1 and Day 2 of Cycle 1, initiated on Day 3 of Cycle 1 and continue for the remainder of the cycle. For each successive cycle, entrectinib will be initiated on Day 1 and continue for the remainder of the 28 day cycle.

Cycle 1 of Treatment (Cycle = 28 Days)

Drug	Dose	Route	Cycle 1 Frequency
PAC-1	TBD	Orally	Day 1 then Day 4 to Day 21; **HELD** Day 2 and Day 3
Entrectinib	600 mg		Day 3 to Day 28; **HELD** Day 1 and Day 2

Cycle 2 and Subsequent (Cycle = 28 Days)

Drug	Dose	Route	Frequency
PAC-1	TBD	Orally	Day 1 to Day 21
Entrectinib	600 mg		Day 1 to Day 28

Study Treatment Dose Levels

Dose Level*	PAC-1 Dose (mg, orally)	Entrectinib (mg, orally)	# of Subjects^
-1	625 daily	400 daily	3-6
1 (starting)	625 daily	600 daily	3-6
2	750 daily	600 daily	3-6

*Pharmacokinetics analysis will be performed at both dose levels during Cycle 1.
^MTD cohort will be initially expanded to 6 patients, and if no DLT move to Phase 2 study.

5.1.1 Dose Escalation Rules and MTD Definition

- Three subjects will initially be enrolled at dose level 1. If none of the 3 subjects experience a dose limiting toxicity (DLT) during the first cycle of therapy, three subjects will be enrolled at dose level 2. If all subjects in dose level 2 complete the first cycle of therapy without DLT, 3 more subjects will be enrolled into dose level 2 to ensure only 0-1 of 6 subjects have a DLT. There will be no further escalation beyond dose level 2.
- Alternatively, if 1 of the first 3 subjects within a dose level cohort experiences a DLT, the cohort will be expanded to 6 subjects. If this happens within dose level 1 and only 1 of the total 6 subjects in dose level 1 experience DLT, the study will proceed to dose level 2. If 2 or more of 6 subjects in a cohort experience DLTs, or 2 subjects within a cohort of 3 subjects experience DLT during the first cycle of therapy (>33% of subjects experiencing DLT), the MTD is exceeded. If this occurs at dose level 1, additional subjects will be accrued to dose level -1. If this occurs at dose level 2, 3 additional subjects will be

enrolled into dose level 1, unless there have been 6 subjects already enrolled into dose level 1.

- The MTD of PAC-1 in combination with entrectinib is the highest tested dose of PAC-1 combined with entrectinib with DLT rate of less than 33% in the first cycle of therapy (i.e., ≤1 out of 6 subjects with DLT). That dose will be recommended for the Phase 2 study.
- At the discretion of the sponsor-investigator, a lower Phase 2 dose may be recommended if other toxicity emerges during the Phase 1b study which does not meet DLT criteria but limits the dose that can be administered cumulatively.

5.1.2 Definition of Dose-Limiting Toxicity

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v.5).

Dose limiting toxicity (DLT) is defined as one of the following events **that are at least possibly related** to study medications occurring during Cycle 1 (first 28 days):

- Grade 3 or greater hematologic toxicity during the first cycle (28 days) of therapy.
- Cerebrovascular ischemia or cerebrovascular hemorrhage of any duration or grade.
- Grade 3 or greater clinical non-hematological toxicity (excluding ≥ grade 3 nausea, vomiting, or diarrhea lasting less than < 72 hours with maximal medical intervention and/or prophylaxis) during the first cycle (28 days) of therapy.
- Delay of Cycle 2 treatment start by more than 2 weeks due to incomplete hematologic recovery (ANC $\geq$ 1.5 x 10^9/L or platelets $\geq$ 100 x 10^9/L) or unresolved treatment related grade 3 or greater non-hematologic toxicity.
- Grade 2 or greater treatment related neurological toxicity occurring during the first cycle of therapy and lasting more than 72 hours.
- Hepatic labs meeting Hy's Law (concomitant elevations of AST/ALT and bilirubin of 3x ULN and 2xULN respectively without alternative etiology)

DLT's will be counted based on the number of patients with DLT at a given dose level, not the absolute number of DLTs. No single patient can trigger more than one DLT event. Additional patient cohorts will not be enrolled until all patients at the current dose level complete all planned treatment for Cycle 1 and are able to start Cycle 2 with no more than a 2-week delay.

Intra-subject dose escalation is not permitted. Once the MTD of PAC-1 in combination with entrectinib is determined, enrollment will continue until at least 6 subjects total are accrued at the maximum tolerated dose.

5.2 Phase 2 Study

At the completion of the phase 1b study, the safety of the PAC-1 and entrectinib combination will be assessed and recommendations will be provided regarding whether to proceed to the phase 2 portion of the study. The sponsor-investigator, Vanquish Oncology, and Genentech will review the DSMB recommendations, and make a decision regarding whether this combination is safe to warrant further study of this combination in a phase 2 study.

The primary objective of the Phase II trial is to determine the activity of the combination of PAC-1 and entrectinib for subjects with uveal melanoma as assessed by PFS at 3 months. Entrectinib, 600 mg orally, will be given Days 1 to Day 28 of each cycle and the recommended phase 2 dose (RP2D) of PAC-1 (PO) will be given on Days 1 to Day 21. Each cycle is 28 days. Treatment will continue until disease progression (based on RECIST 1.1 criteria), unacceptable toxicity, subject withdrawal of informed consent, or subject death either from progression of disease, the therapy itself, or from other causes. Subjects who voluntarily withdrew from study treatment, have progressive disease, or unacceptable toxicities will be followed for survival every 2 months for 12 months from start of study treatment, then every 3 months for up to 24 months.

5.3 Administration of Study Drugs

Criteria for the initiation of a new cycle of treatment can be found in Section 6.1. All tablets are to be ingested as dispensed by research team (e.g. tablets may not be broken or crushed by subject); patients who have difficulty swallowing tablets will be excluded from the study. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. Missed doses will not be made up. A window of ± 3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).

Patients will keep a drug diary to record each dose of the study drugs and time of day when administered, and any side effects they are experiencing. Research staff will record information from the diaries, discuss any concerns the patient has regarding the treatment, and will also collect any unused medication during these visits. Patients will be closely monitored for toxicities and CTCAE v5 will be used to assess toxicities.

5.3.1 Entrectinib

Entrectinib (PO) will be dosed at 600 mg daily in the evening on Days 1-28 of each 28 day cycle (for exception in Cycle 1, see below). During Cycle 1 for each dose cohort, subjects will be instructed to administer their daily dose at the same approximate time (+/- 1 hour) each evening. The study drug will be administered in the evening. Patients will be instructed to take each oral dose of entrectinib with 8 ounces of water (1 cup, 240 mL) and with food.

Entrectinib therapy will be withheld on Days 1 and 2 and initiated during Cycle 1 on Day 3 to continue for the remainder of the cycle. Administration of entrectinib on Days 3 and 21 of Cycle 1 will occur in the morning. Entrectinib administration will occur 1 hour before PAC-1 on Day 21. Information on the time and number of entrectinib doses received for the 96 hours prior to the dose on Day 21 will be obtained from subjects.

5.3.2 PAC-1

In Phase 1b, PAC-1 (PO) will be dosed at 625 or 750 mg daily in the morning on Days 1-21 of each 28 day cycle (for exception in cycle 1, see below). The dose which is determined to be the MTD will be taken in the morning on Days 1-21 of the cycle in Phase 2.

During Cycle 1 for each dose level, subjects will be instructed to administer their daily dose at the same approximate time (+/- 1 hour) each morning. Subsequent cycles must meet the criteria found in section 6.1. The study drug will be administered in the morning and on an empty stomach with the patient remaining NPO (nothing by mouth), except for water and prescribed medications, for 2 hours before and 1 hour after each dose. Patients will be instructed to take each oral dose of PAC-1 with 8 ounces of water (1 cup, 240 mL).

For Cycle 1, PAC-1 will be given on Day 1 and withheld on Days 2 and 3. The dose on these days are being held in order to determine the PK of single-agent entrectinib on Day 3 of the cycle. PAC-1 treatment will be re-initiated on Day 4 and continue to Day 21 of the 28-day cycle. Administration of PAC-1 on Days 1 and 21 of Cycle 1 will occur in the morning. Information on the time and number of PAC-1 doses received for the 96 hours prior to the dose on Day 21 will be obtained from subjects.

5.4 Supportive Care

Optimal care should be given to all subjects. Subjects should receive full supportive care during the study, including transfusion of blood and blood products, treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates, when appropriate. Although acetaminophen at doses of ≤ 2 grams/day is permitted, it should be used with caution in subjects with impaired liver function.

Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. If prophylactic antiemetic therapy is needed, 5-HT3 receptor antagonists (without corticosteroids) should be tried first. Due to the potential of benzodiazepines to cause sedation, the use of benzodiazepines for antiemetic prophylaxis should be reserved for subjects who cannot be satisfactorily managed otherwise. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

5.5 Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the sponsor-investigator by contacting the HCRN Project Manager. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.5.1 Permitted Concomitant Medications

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal medications are allowed. In

general, the use of any concomitant medication deemed necessary for the care of the subject is permitted in this study, except as specifically prohibited below.

The subject must be told to notify the investigational site about any new medications subject takes after the start of the study treatment. All medications (other than study drugs) and significant non-drug therapies (including vitamins, herbal medications, physical therapy and blood transfusions) administered within 30 days of study entry and during the study must be listed on the Concomitant medications/Significant non-drug therapies section of the subject record.

Although acetaminophen at doses of ≤ 2 grams/day is permitted, it should be used with caution in subjects with impaired liver function.

5.6.2 Permitted Concomitant Therapy Requiring Caution

Entrectinib is mainly eliminated through hepatic clearance and CYP3A4 plays a significant role in the biotransformation of entrectinib. Co-administration of strong or moderate CYP3A4 inhibitors and inducers should be avoided. In vitro, entrectinib exhibited potential to inhibit and induce the activities of CYP3A, and potential for inhibition of CYP2C9 and CYP2D6, which suggests a potential for interaction with other drugs metabolized by these isoforms. Because of this, entrectinib should be administered with caution with the drugs listed in Appendix 2.

In addition, since absorption of entrectinib is pH sensitive, patients using H2-receptor antagonists, proton pump inhibitors (PPIs), and/or antacids should discontinue these drugs prior to starting entrectinib. If not possible, or if after discontinuation such therapy needs to be resumed, patients should be instructed to take only H2 receptor antagonists or antacids, if possible, as the duration of action of these drugs is relatively transient compared with PPIs that have longer half-lives, and thus may be administered at safe intervals in relation to entrectinib. These medications should be taken at a time point that is not proximal to entrectinib administration (at least 3-4 hours before or after entrectinib administration).

Medications that prolong QT/QTc interval should be avoided. Subjects that require medications that prolong QT/QTc interval should be monitored closely during treatment.

5.6.3 Prohibited Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy not specified in this protocol
- Concomitant use of chemotherapy
- Investigational agents other than entrectinib or PAC-1
- Radiation therapy
- Herbal medications (e.g., St. John’s Wort)

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management, but not for progressive disease, should be removed from the trial and replaced.

5.7 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting. Patients are to be instructed to refrain from using alcohol while enrolled in this study. Consumption of grapefruit and/or grapefruit juice should be avoided during the treatment period.

5.8 Reproductive Information

Participants of childbearing potential who are sexually active and their partners must agree to (1) abstain from heterosexual intercourse or (2) use 2 forms of effective methods of contraception as outlined below (one from each list).

Primary Forms	Secondary Forms
tubal sterilization (tubes tied)	male latex condom with or without spermicide
partner's vasectomy	diaphragm with spermicide
intrauterine device (IUD)	cervical cap with spermicide
hormonal contraceptives- (includes transdermal patch, injectables, implantables	vaginal sponge (contains spermicide)

Female participants of child bearing potential must agree to use contraception from the time of informed consent, during the study and for 3 months after the last dose of study drug(s). Male participants must agree to use contraception from the time of initiation of study treatment, during the study and for 3 months after the last dose of study drug(s).

6 DOSE DELAYS/DOSE MODIFICATIONS

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v.5). Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring protocol therapy interruption or discontinuation at each study visit for the duration of their participation in the study.

6.1 Start of a New Cycle

A new treatment cycle will only be initiated when all of the following conditions are met:

- ANC $\geq$ 1,500/mm^3
- platelets $\geq$ 100,000/mm^3
- non-hematologic treatment related toxicities have improved to $\leq$ Grade 1 or to the patient's baseline values (except alopecia)

If blood counts are below this threshold, blood work is to be repeated weekly until counts are at an acceptable level. Treatment will be restarted with appropriate dose modifications. If treatment is unable to restart within 4 weeks of the planned treatment date, the patient will be permanently discontinued from study therapy. **NOTE:** For Cycle 1 of the Phase 1b study only, the inability to restart therapy within 2 weeks of the planned date is a DLT (per section 5.1.2); however the patient is allowed an additional week of recovery and is allowed to remain on study if treatment restarts within 4 weeks.

For subjects who present to the clinic with toxicity during a current treatment cycle, the study drug may be stopped per the discretion of the site investigator if the toxicity is determined to be clinically significant.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient subject vacation, and/or holidays). Subjects should be placed back on study therapy within 4 weeks of the scheduled interruption, unless otherwise discussed with the sponsor-investigator. The reason for interruption should be documented in the patient's subject's study record.

6.2 Dose Modifications for PAC-1 Toxicity

CTCAE v 5 Adverse Effects Terms & Descriptions)	**PAC-1 Dose Modifications**
Any other grade 3 non-hematologic toxicity	Hold dose until improvement to grade ≤ 1 then decrease dose by one dose level below level that caused toxicity.
Grade ≥ 2 neurologic toxicity detected at any time while on study treatment	Hold dose until improvement to grade ≤ 1 then decrease dose by one dose level below level that caused toxicity.
Any grade cerebrovascular ischemia or hemorrhage	Discontinue treatment.
Any other grade 4 non-hematologic toxicity	Discontinue treatment.
Neutrophils < 500 cells/mm^3	Hold dose until improvement to grade ≤ 1 then decrease dose by one dose level below level that caused toxicity.
Febrile Neutropenia	Hold dose until improvement to grade ≤ 1 then decrease dose by one dose level below level that caused toxicity.
Platelets < 25,000/mm^3or platelets < 50,000/mm^3 with bleeding	Hold dose until improvement to grade ≤ 1 then decrease dose by one dose level below level that caused toxicity.
Any other grade 3 hematologic toxicity	Hold dose until improvement to grade ≤ 1 then decrease dose by one dose level below level that caused toxicity.
Any other grade 4 hematologic toxicity	Discontinue treatment.

6.2.1 PAC-1 Dose Reduction

Dose Reduction[a,b,c]	Dose	Dose
Starting Dose	750 mg daily	625 mg daily
First Dose Reduction	625 mg daily	500 mg daily
Second Dose Reduction	500 mg daily	375 mg daily
Third Dose Reduction	375 mg daily	250 mg daily
Fourth Dose Reduction	250 mg daily	NA

[a] In the event a dose modification is needed, initiation of re-treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity
[b] If the patient has not recovered after a 2-week delay, discontinue treatment
[c] Up to four dose reductions are allowed if the starting dose is 750 mg. If subsequent cycles require additional dose reductions, treatment will be discontinued.

6.3 Dose Modifications for Entrectinib Toxicity

Dose Modifications for Entrectinib-Related Adverse Events

Toxicity*	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity is ≤ G1 or has returned to baseline, then reduce by 1 dose level and resume treatment	Withhold dose until toxicity is ≤ G1 or has returned to baseline, then reduce by 1 dose level and resume treatment; or discontinue treatment as per the Investigator's discretion
Central Nervous System Effects	Continue at same dose level	Intolerable Grade 2; Withhold dose until recovery to ≤ Grade 1 or to baseline. Resume at same dose or reduced dose, as clinically appropriate.	Withhold dose until recovery to ≤ to Grade 1 or to baseline. Resume at same dose or reduced dose, as clinically appropriate.	Discontinue treatment permanently

Hematologic	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity is ≤ G2, or has returned to baseline, then resume treatment at the same dose level or reduce by 1 dose level as per the Investigator's discretion Grade 3 lymphopenia without other dose-limiting events (e.g., opportunistic infection) may continue study treatment without interruption	Withhold dose until toxicity is ≤ G2, or has returned to baseline, then reduce the dose by 1 dose level and resume treatment Grade 4 lymphopenia without other dose-limiting events (e.g., opportunistic infection) may continue study treatment without interruption
QT Interval Prolongation	QTc greater than 500 ms	Withhold entrectinib until QTc interval recovers to baseline. Resume at same dose if factors that cause QT prolongation are identified and corrected. Resume at reduced dose if other factors that cause QT prolongation are not identified.		
	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	Permanently discontinue entrectinib		
Vision Disorders	Grade 2 or above	Withhold entrectinib until improvement or stabilization. Resume at same dose or reduced dose, as clinically appropriate.		
Anemia or neutropenia	Grade 3 or 4	Withhold entrectinib until recovery to less than or equal to Grade 2. Resume at the same dose or reduced dose, as clinically appropriate.		
Congestive heart failure	Continue at same dose level	Withhold dose until toxicity is ≤ G1 or has returned to baseline, then reduce by 1 dose level and resume treatment	Withhold dose until toxicity is ≤ G1 or has returned to baseline, then reduce by 1 dose level and resume treatment	Discontinue treatment permanently

<table>
<tr><td>Pneumonitis (in absence of disease progression, pulmonary embolism, positive cultures or radiation effect)</td><td>Withhold dose until toxicity is Grade 0, then resume treatment at same dose
Discontinue treatment permanently if pneumonitis recurs</td><td>Withhold dose until toxicity is Grade 0, then resume treatment at same dose
Discontinue treatment permanently if pneumonitis recurs</td><td>Discontinue treatment permanently</td><td>Discontinue treatment permanently</td></tr>
<tr><td>Hyperuricemia symptomatic or Grade 4</td><td colspan="4">Initiate urate-lowering medication.
• Withhold entrectinib until improvement of signs or symptoms.
• Resume entrectinib at same or reduced dose.</td></tr>
<tr><td rowspan="2">Hepatotoxicity</td><td>Continue at same dose level</td><td>Continue at same dose level</td><td>Withhold dose until recovery to ≤ to Grade 1 or to baseline.

Resume at same dose if resolution occurs within 4 weeks.

Permanently discontinue if adverse reaction does not resolve within 4 weeks.

Resume at a reduced dose for recurrent Grade 3 events that resolve within 4 weeks.</td><td>Withhold dose until recovery to ≤ to Grade 1 or to baseline.

Resume at same dose if resolution occurs within 4 weeks.

Permanently discontinue if adverse reaction does not resolve within 4 weeks.

Permanently discontinue for recurrent Grade 4 events</td></tr>
<tr><td colspan="4">ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 1.5 times ULN (in the absence of cholestasis or hemolysis) permanently discontinue treatment.</td></tr>
<tr><td>Other Clinically Relevant Adverse Reactions</td><td>Grade 3 or 4</td><td colspan="3">Withhold entrectinib until adverse reaction resolves or improves to recovery or improvement to Grade 1 or baseline.

Resume at the same or reduced dose, if resolution occurs within 4 weeks.

Permanently discontinue if adverse reaction does not resolve within 4 weeks.

Permanently discontinue for recurrent Grade 4 events.</td></tr>
</table>

*dose modifications to be based on worst toxicity grade as per NCI CTCAE v5.0

6.3.2 Entrectinib Dose Reduction

Dose Reduction[a,b,c]	Dose
Starting Dose	600 mg daily
First Dose Reduction	400 mg daily
Second Dose Reduction	200 mg daily

[a] In the event a dose modification is needed, initiation of re-treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity
[b] If the patient has not recovered after a 2-week delay, discontinue treatment
[c] Two dose reductions are allowed. If subsequent cycles require additional dose reductions, treatment will be discontinued.

6.4 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined above, a subject will also be discontinued from protocol therapy and followed per protocol under the following circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF)

- If there is evidence of disease progression
- If the treating physician thinks a change of therapy would be in the best interest of the subject
- If the subject requests to discontinue protocol therapy
- If the protocol therapy exhibits unacceptable toxicity
- If a female subject becomes pregnant
- If there is a $\geq$ 4 week delay between cycles due to a treatment related adverse event.
- Subjects can stop study participation at any time. However, if they decide to stop, subjects will continue to be followed as per Section 7 calendar

6.5 Protocol Discontinuation

If a subject decides to discontinue from the protocol (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. A complete final evaluation at the time of the subject's protocol withdrawal should be made with an explanation of why the subject is withdrawing from the protocol. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7 STUDY CALENDAR & EVALUATIONS

Study Evaluation Cycle = 28 days	Screening	Cycle 1	Cycle 2 and Subsequent	Safety follow up visit[12]	Long-term Follow up[13]
	-28 days	Day 1 ± 3 days	Day 1 ± 3 days	30 days post last dose	Every 2-3 months
REQUIRED ASSESSMENTS					
Informed Consent	X				
Medical History[1]	X				
Diagnosis and Disease Staging[1]	X				
Physical Exam[2]	X	X	X	X	
Vital signs and ECOG Performance Status[2]	X	X	X	X	
ECG[3]	X	X[3]	X[3]	X	
ECHO[3]	X				
Mini Mental Status Exam (MMSE) and Neurologic exam[4]	X	X	X[4]	X[4]	
AEs & concomitant medications	X	X	X	X	
LABORATORY ASSESSMENTS					
Complete Blood Cell Count with diff (CBC)	X	X[11]	X	X	
Comprehensive Metabolic Profile (CMP)[5]	X	X[11]	X	X	
Ammonia, Lactate Dehydrogenase and Uric Acid[5]	X	X[11]	X		
PT/INR and aPTT[5]	X				
Pregnancy test (serum or urine) (WOCBP)[5]	X	X[5]			
Urinalysis[5]	X				
DISEASE ASSESSMENT					
CT of chest[6]	X		X[6]		X[6]
CT or MRI of abdomen and pelvis[6]	X		X[6]		X[6]
MRI Brain[6]	X[6]				
TREATMENT EXPOSURE					
PAC-1[7]		X[7]	X[7]		
Entrectinib[7]		X[7]	X[7]		
SPECIMEN COLLECTION					
Plasma for PAC-1 PK/PD[8]		X[8]			
Plasma for Entrectinib PK/PD[8]		X[8]			
Blood sample for somatic baseline[9]		X[9]			
Blood samples for CTCs, MOA and ctDNA[9]		X[9]	C2D1	X[9]	
Archival or Fresh Tumor Tissue[10]	X[10]	X[10]			
FOLLOW-UP					
Survival Status, Subsequent Therapy					X

Key to Footnotes

1: Medical History including all prior anti-cancer treatment. Other data to obtained during this assessment includes a smoking history questionnaire and trial awareness question. Diagnosis and staging to include pathology report and TNM staging documentation. AJCC manual Edition 8.

2: During the physical exam if the subject is experiencing visual changes, further investigation may be warranted with an ophthalmologic exam including at least the visual acuity and slit-lamp tests. This determination will be at the discretion of the site investigator. Vital signs to include temperature, pulse, respirations, blood pressure weight, and height (screening only) and ECOG performance status.

3: ECG will be performed at screening then Day 1 of each Cycle. An ECHO will be performed at screening to assess LVEF. Testing during and after study treatment is at the discretion of the site investigator.

4: A basic neurologic exam will be performed by the site investigator at screening, Day 1 of each Cycle of treatment and at the D30 safety follow up visit to monitor for neurologic toxicity. The Mini Mental Status Exam (MMSE) will be performed by a member of the research staff at screening and Day 1 of each Cycle of treatment to monitor for cognitive toxicity. The results of the MMSE and neurologic exam will be reviewed by the site investigator who will determine whether dose reduction of study drug(s) is required. This information should be retained.

5: CBC with differential and platelet to include: WBC, ANC, ALC, Hgb, PLT. Comprehensive metabolic profile (CMP) will be done at screening then Day 1 of each Cycle. During Cycle 1, a CMP should be performed at Cycle 1 Day 15. CMP to include glucose, calcium, BUN, creatinine, sodium, potassium, chloride, serum albumin, total bilirubin, alkaline phosphatase, AST, and ALT, ammonia, LDH and uric acid. Coagulation studies (PT/INR and PTT) will be done at screening then at the discretion of the treating investigator during treatment. For women of childbearing potential (WOCBP): urine or serum βhCG if clinically appropriate. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Testing is required within 72 hours prior to initiation of study treatment. Urinalysis will be performed at screening.

6: Tumor response assessment will consist of evaluation by CT scans of chest and MRI or CT of abdomen and pelvis at screening and every odd numbered cycle starting after screening with CT scan before Cycle 3 (imaging selected for each subject should remain the same throughout the study); tumor imaging to be done at the safety follow up visit is at discretion of site investigator. If tumor assessments are available for subjects who have not yet experienced progressive disease (PD) at the time treatment is discontinued, the follow-up tumor evaluations will be documented in the eCRF until PD or death is confirmed, or until another treatment is initiated. MRI of the brain will be performed per standard of care for those subjects with a history of brain metastasis. A window of - 7 days may be used. CT/MRI images are to be submitted for central analysis. Images will be de-identified prior to sending to a central location. Central analysis to be performed upon receipt of funding.

7: Cycle = 28 days. PAC-1 will be taken once daily, Days 1-21. For Cycle 1, PAC-1 will be given on Day 1 and withheld on Days 2 and 3. The dose on these days is being held in order to determine the PK of single-agent entrectinib on Day 3 of the cycle. PAC-1 treatment will be re-

initiated on Day 4 and continue until Day 21 of the 28 day cycle. Administration of PAC-1 on Days 1 and 21 of Cycle 1 will occur in the morning. Entrectinib will be taken once daily, Days 1-28. Entrectinib therapy will be withheld on Days 1 and 2 and initiated during Cycle 1 on Day 3 to continue until Day 28 of the 28 day cycle. Administration of entrectinib on Days 3 and 21 of Cycle 1 will occur in the morning. Entrectinib administration will occur 1 hour before PAC-1 on Day 21.

8: The PK and PD analyses will occur with each dose level during Phase Ib. Pharmacokinetic and pharmacodynamic sample collections will occur in the mornings on Day 1(PAC-1 only), Day 3 (entrectinib only), and Day 21 (PAC-1 and entrectinib) of the first cycle. Day 1 Cycle 1: Subjects receive only PAC-1. Blood samples are collected immediately prior to oral ingestion of PAC-1 and at the following time points after ingestion: 0.5, 1, 2, 3, 4, 6, 7, and 24 hours. Day 3 Cycle 1: Subjects receive only entrectinib. Blood samples are collected immediately prior to oral ingestion of entrectinib and at the following time points after ingestion: 0.5, 1, 2, 3, 4, 6, 7, and 24 hours. Day 21 Cycle 1: Subjects receive both PAC-1 and entrectinib. Entrectinib will be taken 1 hour before PAC-1. Blood samples are collected immediately prior to oral ingestion of entrectinib, 0.5 hour before ingestion of PAC-1, and at the following time points after ingestion of PAC-1: 0.5, 1, 2, 3, 4, 6, 7, and 24 hours. See Correlative Laboratory Manual (CLM) for additional details regarding these samples.

9: Subject consent will be obtained for collection of peripheral blood samples prior to treatment on Cycle 1 Day 1, Cycle 2 Day 1 and at progression (safety visit). For subjects who come off treatment due to progression, the sample may be obtained during the safety visit. Specimens will be used for analysis of circulating tumor cells (CTCs), analysis related to mechanisms of action as well as ctDNA. Somatic baseline testing will be performed prior to treatment Cycle 1 Day 1. Blood that is leftover after initial protocol specific testing is performed will be stored for future correlative testing as described in Section 8. See CLM for additional details regarding these samples.

10: Archival tissue (metastatic disease preferred) is required if available and should be identified at screening and shipped prior to Cycle 1 Day 1. If archival tissue is not available, a biopsy is required prior to Cycle 1 Day 1 treatment (Cap of 15 biopsies). Tissue that is leftover after initial protocol specific testing is performed will be stored for future correlative testing as described in Section 8. See CLM for additional details regarding these samples.

11: If screening (baseline) CBC, CMP, magnesium, Lactate Dehydrogenase, uric acid and PT/PTT/INR were performed within 7 days of Cycle 1 Day 1 of treatment, these do not need to be repeated. All laboratory assessments should be done prior to treatment.

12: Safety Follow Up: The safety follow-up visit should only occur when subjects permanently stop study treatment for whatever reasons (toxicity, progression, or other reason) and should be performed 30 days (+ 7 days) after the last dose of treatment. Subjects with unresolved treatment-related toxicity should be followed as medically appropriate or until stabilization of toxicity.

13: Long Term Follow Up: Radiographic disease assessment should be performed at physician discretion. Subjects will be followed for survival every 2 months (+14 days) for 12 months from Cycle 1 Day 1 then every 3 months (+21 days) for up to 24 months. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate.

8. CORRELATIVE STUDIES AND PROCEDURES

Please see the correlative laboratory manual (CLM) for additional details about the correlatives described below. The analyses described below will be performed upon receipt of funding.

8.1 Peripheral Blood Samples

8.1.1 Plasma for Pharmacokinetics and Pharmacodynamics

In phase 1b, the pharmacokinetics (PK) and pharmacodynamics (PD) of PAC-1 will be assessed following doses administered on Days 1 and 21 of the first cycle. In phase 1b, the PK and PD of entrectinib will be assessed following the dose administered on Days 3 and 21 of the first cycle. Entrectinib will be withheld on Days 1 and 2 to allow assessment of PAC-1 PK when administered as single agent. PAC-1 will be withheld on Days 2 and 3 to allow assessment of entrectinib PK when administered as single agent on Day 3. PKs of both drugs will be assessed on Day 21 to determine effects of repeated dosing or combining of the two drugs. The PK and PD analyses will occur with each dose level.

Administration of PAC-1 on Days 1 and 21 and entrectinib on Days 3 and 21 of Cycle 1 will occur in the morning. Entrectinib administration will occur 1 hour before PAC-1 on Day 21. The dose timing on this day is being specified to accommodate a sampling schedule that minimizes the number of blood draws needed from the patient. Information on the time and number of PAC-1 and entrectinib doses received for the 96 hours prior to the dose on Day 21 will be obtained from subjects. Patients will not receive their PAC-1 dose on Days 2 and 3 of Cycle 1. The doses on these days are being held in order to accurately define the absorption and metabolism of entrectinib when administered as a single agent on Day 3. Likewise, patients will not receive their entrectinib dose on Days 1 and 2 of Cycle 1. The doses on these days are being held in order to accurately define the absorption and metabolism of PAC-1 when administered as a single agent on Day 1. Actual and nominal sample collection times will be recorded on the case report forms and sample tubes.

Sample collections will occur in the mornings on Day 1 (PAC-1 only), Day 3 (entrectinib only), and Day 21 (PAC-1 and entrectinib) of the first cycle.

- Day 1, Cycle 1: Subjects receive only PAC-1.
  - Blood samples are collected immediately prior to oral ingestion of PAC-1 and at the following time points after ingestion: 0.5, 1, 2, 3, 4, 6, 7, and 24 hours.
- Day 3, Cycle 1: Subjects receive only entrectinib.
  - Blood samples are collected immediately prior to oral ingestion of entrectinib and at the following time points after ingestion: 0.5, 1, 2, 3, 4, 6, 7, and 24 hours.
- Day 21, Cycle 1: Subjects receive both PAC-1 and entrectinib.
  - Entrectinib administered 1 hour before PAC-1.
  - Blood samples are collected immediately prior to oral ingestion of entrectinib, 0.5 hour before ingestion of PAC-1, and at the following time points after ingestion of PAC-1: 0.5, 1, 2, 3, 4, 6, 7, and 24 hours. The sample volume is 10-mL at each time point.

8.1.1.1 Pharmacokinetic Analysis

Non-compartment analysis: Non-compartmental analysis of the PAC-1 plasma concentration-time data following doses on Days 1 and 21 for Cycle 1 for each dose level. Also on Days 3 and 21 of Cycle 1, entrectinib plasma concentration data will be performed using WinNonlin 6.3 (Pharsight, St Louis, MO) for subjects in whom complete PK profiles are obtained. Pharmacokinetic parameters to be estimated following each dose include: 1). area under the PAC-1 plasma concentration-time curve from time 0 to 24 hours (AUC_{0-24}) for days 1 and 21, 2) area under the entrectinib plasma concentration-time curve from 0 to 24 hours (AUC_{0-24}) for Days 3 and 21, 3). area under the PAC-1 plasma concentration-time curves from time 0 to infinity ($AUC_{0-\infty}$) on Day 1 only, 4). area under the entrectinib plasma concentration-time curves from time 0 to infinity ($AUC_{0-\infty}$) on Day 3 only, maximum PAC-1 and entrectinib plasma concentrations (C_{max}), 5). terminal elimination rate constant for both drugs (λ_z), and 6). oral clearance (CL/F) for both drugs.

Statistical Analysis: The influence of multiple dosing (e.g., PAC-1 Day 1 $AUC_{0-\infty}$ vs. Day 21 AUC_{0-24} and entrectinib Day 3 $AUC_{0-\infty}$ vs. Day 21 AUC_{0-24}), concurrent administration of PAC-1 and dose on the pharmacokinetics of entrectinib (e.g., Day 3 $AUC_{0-\infty}$ vs. Day 21 AUC_{0-24}), and concurrent administration of entrectinib and dose on the pharmacokinetics of PAC-1 (e.g., Day 1 $AUC_{0-\infty}$ vs. Day 21 AUC_{0-24}), will be evaluated using a generalized linear models approach. PAC-1 AUC_{0-24}, $AUC_{0-\infty}$, C_{max} and CL/F will be log transformed before statistical analysis. Entrectinib AUC_{0-24}, $AUC_{0-\infty}$, C_{max} and CL/F will be log transformed before statistical analysis. Geometric means will be calculated for the parameters on each study day. The 90% confidence intervals for the geometric mean ratios will be constructed for every comparison.

8.1.1.2 Pharmacodynamic Assessment

The pharmacodynamic (PD) effects of PAC-1 (Days 1 and 21 of Cycle 1), and entrectinib (Days 3 and 21 of Cycle 1), may be used to assess the systemic responses of individuals following PAC-1 or entrectinib doses administered orally. Systemic variables are defined as plasma concentrations of PAC-1 or entrectinib, which will be measured and used to assess whether PAC-1 or entrectinib has affected the production of these biological markers. Measures of toxicity (e.g., changes in WBC counts, differential cell populations, platelets, etc.) are also considered systemic PD variables.

8.1.2 Mechanisms of Action Analysis

Subject consent will be obtained for collection of peripheral blood samples for whole blood, plasma and serum prior to treatment on Cycle 1 Day 1, Cycle 2 Day 1 and at progression (safety visit). This specimen will be used for analysis related to Mechanisms of Action.

8.1.3 Circulating Tumor Cells (CTCs)

Subject consent will be obtained for collection of peripheral blood samples prior to treatment on Cycle 1 Day 1, Cycle 2 Day 1 and at progression (safety visit). This specimen will be analyzed for total CTCs. Spearman correlation will be computed using PROC CORR in SAS (Cary, NC). CTC number or change from Cycle Day 1 to Cycle 2 Day 1 will be correlated with ORR assessed by imaging (revised RECIST 1.1 criteria). Spearman correlation will be computed using PROC CORR in SAS (Cary, NC).

8.1.4 Somatic Baseline
Whole blood will be collected prior to treatment Cycle 1 Day 1 for somatic baseline testing.

8.1.5 Plasma for ctDNA
Subject consent will be obtained for collection of peripheral blood samples for ctDNA prior to treatment on Cycle 1 Day 1, Cycle 2 Day 1 and at progression (safety visit).

8.2 Tissue Samples

8.2.1 Archival or Fresh Tissue
Archival tumor tissue (metastatic disease preferred) is required if available and should be identified at screening and shipped by Cycle 1 Day 1. If archival tissue is not available, a biopsy is required prior to Cycle 1 Day 1 of treatment. There is a cap of 15 biopsies.

8.2.2 Immunohistochemistry (IHC)
IHC for markers such as but not limited to procaspase 3. Determine correlation between procaspase 3 expression in tumor tissue and clinical **response.** Procaspase 3 expression will be correlated with ORR assessed by imaging (revised RECIST 1.1 criteria). Spearman correlation will be computed using PROC CORR in SAS (Cary, NC).

8.2.3 Imaging
Imaging may also be performed in an effort to elucidate aspects of the mechanism of action.

8.2.4 Genomic Analysis
Genomic analysis may also be performed in an effort to elucidate aspects of the mechanism of action.

8.3 Confidentiality of Biospecimens
Samples that are collected will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

8.4 Storage of Biospecimens
Remaining specimens once protocol described biospecimen-based studies are complete will be stored for future unspecified cancer related research after consent is obtained from subjects.

9. CRITERIA FOR DISEASE EVALUATION
Tumor response will be defined by the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.[21]

9.1 Measurable Disease
The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

9.2 Measurable Lesions

Measurable lesions are defined as the presence of at least one measurable lesion. 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, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.3 Non-measurable Lesions

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 subject, these are preferred for selection as target lesions.

9.4 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.

9.5 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.

9.6 Evaluation of Target Lesions

NOTE: Please see the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment 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

9.7 Evaluation of Non-target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level.
Incomplete Response/Stable Disease	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor-investigator.

9.8 Evaluation of Best Overall Response

NOTE: Revise table if response rate is primary objective of the study, and confirmation of response is required. See Eur J Cancer 45;2009:228-247 for complete details.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response****
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			
All responses will require confirmation with repeat imaging or physical exam at ≥ 4 weeks.			

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

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

9.9 Definitions for Response Evaluation

9.9.1 Duration of Response

Duration of response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

9.9.2 Objective Response Rate

The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.9.3 Progression-Free Survival

A measurement from the date of the start of treatment until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

9.9.4 Overall Survival

Overall survival is defined by the date of the start of treatment to date of death from any cause.

10. DRUG INFORMATION

10.1 PAC-1

Please refer to the current version of the Investigator's Brochure (IB) for additional information regarding this drug.

10.1.1 Classification

Ortho-hydroxyl *N*-acyl hydrazone that enhances the enzymatic activity of procaspase-3 and induces apoptosis in cancer cells.

10.1.2 Availability

PAC-1 will be provided by Vanquish Oncology, Inc. with approval of the FDA for investigational purposes (IND# 120544).

10.1.3 Description
PAC-1 will be provided in strengths of 250 mg tablets. Each tablet contains PAC-1 in combination with Avicel PH 101 & 200 (microcrystalline cellulose filler, NF), Pearlitol 100 SD (mannitol filler, USP), Explotab (sodium starch glycolate disintegrant, NF), Cabosil (fumed silica glidant, NF), hydroxypropyl cellulose (binder, NF) and Sodium Stearyl Fumarate (lubricant, NF). PAC-1 tablets will be supplied to the experimental pharmacy where the correct dose for one cycle will be packaged for each patient.

10.1.4 Storage, Handling and Accountability
Bottles containing PAC-1 tablets will be provided to the investigative site. Bottles will be stored at room temperature, 15ºC to 27ºC upon arrival at the site. A packing list will be included with the shipment of clinical study material. Upon receipt of study drug, the site will inspect the shipment for any damage, and compare contents against the packing list. The site will acknowledge receipt of the shipment by contacting Vanquish Oncology, Inc., noting any discrepancies or damages.

10.1.5 Dosage and Administration
Doses of 625 and 750 mg will be tested in the Phase 1b study and the RP2D will be tested in the Phase 2 study. Tablets are taken with water.

PAC-1 will be supplied as 250 mg dose with a 125 mg dose score mark tablets. Approximately 1000 tablets are bulk-packaged into 950 cc HDPE Bottles with five 1-Gram desiccant packets per bottle, capped with 53 mm child-resistant closures with FS M1/.035 Pulp Liner, induction sealed, and labeled. Tablets will be distributed to patients by licensed pharmacist according to the clinical protocol and the separate Investigator Brochure.

10.1.6 Side Effects
The risks of oral PAC-1 in humans are unknown. However, PAC-1 has shown toxicity in mice, rats, and dogs. In a rat study, deaths occurred in 2 out of 12 rats administered 600 mg/kg/day over a 7-day interval – it should be noted this is a dose over 10 times higher than the planned maximum daily dose to be tested in this trial, 3000 mg (i.e., 50 mg/kg for a 60 kg individual). In one dog study involving repeated oral dosing of PAC-1, gastro-intestinal symptoms were observed (diarrhea, vomiting) accompanied by weight loss. As well, one of the dogs in that study had a seizure that was resolved by administration of diazepam. In another dog study, daily administration of oral PAC-1 at doses of 25 and 50 mg/kg for 28 days was associated with minimal-mild neurodegeneration at multiple sites in the gray matter of the cerebrum. An 84-day oral toxicity and toxicokinetic study of PAC-1 with 1 month and 3 months recovery periods in male and female beagle dogs was recently completed. Daily oral administration (via capsules) of PAC-1 at 6, 13, or 25 mg/kg for 21 consecutive days with a 7-day wash-out period between cycles and repeated for 3 cycles dose-responsive, minimal to mild test article-related vacuolation in different sections of the brains of animals given 13 and 25 mg/kg. The extent and severity of the vacuolization was similar to that seen in the 28-day study. The observed brain vacuolization did not show evidence of recovery after 3 months of being off study drug. No PAC-1 associated neurological or neurocognitive changes have been observed through dose level 7 (750 mg) of Component 1 of phase 1 study NCT02355535.

10.1.7 Warnings and Precautions

Observation and assessment of hematological and non-hematological markers of toxicity in research dogs raised a possibility that PAC-1 may cause neurodegenerative changes in the brain, and therefore neurological and neurocognitive examinations was performed in NCT02355535 study. No neurologic nor neurocognitive changes were seen in this study, therefore these evaluations will not be performed in this study.

In NCT02355535 (Procaspase Activating Compound-1 (PAC-1) in the Treatment of Advanced Malignancies - Component 1), one Component 1 patient who was in the 625mg/day cohort experienced an intracranial hemorrhage related to brain metastases where a possible attribution to PAC-1 could not be ruled out. In order to monitor and ensure patient safety, patients should have a baseline brain MRI for future comparison if needed. Coagulation tests will be done prior to dosing on Day 1 of each treatment cycle.

10.2 Entrectinib

Please refer to the current version of the IB for additional information regarding this drug.

10.2.1 Classification

Entrectinib is an approved in United States for the treatment of locally advanced or metastatic solid tumors that harbor NTRK1/2/3 or ROS1 gene fusions. It is a selective, CNS-active tyrosine kinase inhibitor designed to inhibit the kinase activity of the TRKA/B/C and ROS1 proteins, whose activating fusions drive proliferation in certain types of cancer. Entrectinib can block ROS1 and NTRK kinase activity and may result in the death of cancer cells with ROS1 or NTRK gene fusions.

10.2.2 Availability

Genentech will supply entrectinib at no charge to subjects participating in this clinical trial. The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.2.3 Description

Entrectinib will be provided as white size 2 and 0 hydroxypropyl methylcellulose (HPMC) capsules. Each capsule contains the following compendial excipients: tartaric acid (acidulant), lactose anhydrous, hydroxypropyl methylcellulose, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, and magnesium stearate. Entrectinib capsules will be supplied to the experimental pharmacy where the correct dose for one cycle will be packaged for each patient.

10.2.4 Storage, Handling and Accountability

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Entrectinib must be stored in the original packaging at controlled room temperature (please refer to the bottle label for more specific expiry and storage conditions). Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

10.2.5 Dosage and Administration

An entrectinib dose of 600 mg will be tested in the Phase 1b and Phase 2 studies. Capsules are taken with water and food.

Entrectinib will be supplied as 200 and 400 mg capsules. Entrectinib capsules are packaged in white high-density polyethylene bottles with child resistant closures and a tamper-proof heat induction seal. Capsules will be distributed to patients by licensed pharmacist according to the clinical protocol and the separate Investigator Brochure.

10.2.6 Side Effects

Please refer to the current version of the Investigator's Brochure for a complete list of adverse events.

11. ADVERSE EVENTS

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern. The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity.

11.1 Definitions

11.1.1 Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with uveal melanoma that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

11.1.2 Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death). **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization. Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE. Hospitalizations for the following reasons do not require reporting:
    - Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
    - Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
    - Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the study drug.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).
    - See Section 11.8 for additional descriptions of reportable events

11.1.3 AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the study drug, for which ongoing monitoring and rapid communication by the site investigator to the sponsor-investigator is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the sponsor-investigator to other parties (e.g., Regulatory Authorities) may also be warranted.

11.1.3.1 The Entrectinib Events of Special Interest are

- Grade ≥ 2 Congestive Heart Failure
- Grade ≥ 2 QT Prolongation
- Any grade syncope
- Grade ≥ 2 cognitive disturbances
- Any grade fracture

11.1.3.2 The PAC-1 Events of Special Interest are

- Grade ≥ 3 Neurologic disturbances
- Grade ≥ 3 Cognitive disturbances

11.1.3.3 Non drug specific adverse events of special interest for this study include the following

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
  - Treatment-emergent ALT or AST > 3 X ULN in combination with total bilirubin > 2 X ULN
  - Treatment-emergent ALT or AST > 3 X ULN in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study drug, as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

11.2 Other Definitions

11.2.1 Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

11.2.2 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

11.2.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.2.4 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Relatedness should be assessed for both study drugs individually. Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is ***not related*** to the study drug(s)
Unlikely	Adverse Event is ***doubtfully related*** to the study drug(s)
Possible	Adverse Event ***may be related*** to the study drug(s)
Probable	Adverse Event is ***likely related*** to the study drug(s)
Definite	Adverse Event is ***clearly related*** to the study drug(s)

11.2.5 Assessment of Severity

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. The following table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
NOTE: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a) Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b) Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c) If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d) Grade 4 and 5 events must be reported as serious adverse events

11.3 Reporting

11.3.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 90 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.

11.3.2 Serious Adverse Events (SAEs) and AESIs

11.3.2.1 Site Requirements for Reporting SAEs and AESI's to HCRN

- SAEs and AESI's will be reported from time of signed informed consent until 90 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs and AESI's will be reported on the SAE Submission Form **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.

The site will submit the completed SAE Submission Form to HCRN **within 1 business day** of discovery of the event**.** The form will be submitted to HCRN electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements. The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site. Once the SAE has resolved, sites must submit a follow-up SAE Submission Form within a reasonable timeframe to HCRN electronically to safety@hoosiercancer.org.

11.3.2.2 HCRN Requirements for Reporting SAEs and AESI's to Vanquish and Genentech/Roche

HCRN will report all SAEs and AESI's to Vanquish and Genentech **within 1 business day** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to Vanquish and Genentech as it is received from site.

Contact information for Genentech/Roche
Attn: Worldwide Product Safety; FAX 650-238-6067 OR Email: usds_aereporting-d@gene.com.

Contact information for Vanquish Oncology, Inc. **Attn: Product Safety; FAX 855 250-2953**
Email: vodrugsafety@vanquishoncology.com

11.4 Sponsor-Investigator Responsibilities

HCRN will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.5 HCRN Responsibilities to FDA

If an IND is assigned, HCRN will manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. HCRN will cross-reference this submission to Vanquish and Genentech's parent IND at the time of submission.

For protocols conducted under an IND, HCRN will be responsible for all communication with the FDA in accordance with 21CFR312 including but not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report.

11.6 IND Safety Reports Unrelated to This Trial

Genentech and Vanquish Oncology, Inc. will provide to HCRN IND safety reports from external studies that involve the study drug(s) per their guidelines. HCRN will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

11.7 Other Reportable Events

11.7.1 Pregnancy

If a female subject becomes pregnant while receiving the study drugs or within 90 days after the last dose of study drugs, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drugs or within 90 days after the last dose of study drugs, a SAE report should be completed and expeditiously submitted within the timeframe described in the SAE reporting section. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE. Sites will report to HCRN **within 1 business day** and HCRN will report to Funders **within 1 business** day.

11.7.2 Special Situation Reports

Special Situation Reports should be collected **even in the absence of an Adverse Event.** Sites will report to HCRN **within 1 business day** and HCRN will report to Funders **within 1 business day.**

- Data related to the product usage during breastfeeding

- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)

In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population.

11.7.3 Product Complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial. All Product Complaints (with or without an AE) shall be forwarded to HCRN who will report to Genentech and Vanquish. The timeframe from the site reporting to HCRN and HCRN reporting to Genentech and Vanquish must be **within fifteen (15) calendar days** of the awareness date.

Genentech/Roche
Product complaints with an AE: Worldwide Product Safety; FAX 650-238-6067 **OR** Email: usds_aereporting-d@gene.com.

Product complaints without an AE: kaiseraugst.global_impcomplaint_management@roche.com

Vanquish Oncology, Inc.
Drug Safety: Fax: (855) 250-2953 or or at vodrugsafety@vanquishoncology.com.

11.7.4 Post-Study Adverse Events

After the end of the adverse event reporting period (defined as 90 days after the last dose of study drug) all deaths, (regardless of cause), and any serious adverse event believed to be related to prior exposure to study drug will be reported from the site to HCRN and HCRN to the Funders. This will include development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject (including pregnancy occurring in the partner of a male study subject).

12. STATISTICAL CONSIDERATIONS

12.1 Study Design

This is a single arm study.

Phase 1b: The primary objective of the Phase Ib dose escalation cohort study is to establish the MTD of PAC-1 in combination with entrectinib in subjects with metastatic uveal melanoma. A standard “3+3” design will be used to establish the MTD. PAC-1 (PO) will be given daily on Days 1 through 21 of each cycle. Entrectinib (PO) will be given daily on Days 1 through 28 of each cycle. Each cycle will equal 28 days. Response will be evaluated after every 2 cycles. Treatment will continue until disease progression based on RECIST criteria or intolerable toxicity.

Phase 2: The primary objective of the Phase II trial is to estimate 3 months PFS using RECIST v1.1 in subjects with metastatic uveal melanoma treated with PAC-1 in combination with entrectinib. PAC-1 (PO) will be given daily on Days 1 through 21 of each cycle. Entrectinib (PO) will be given daily on Days 1 through 28 of each cycle. Each cycle will equal 28 days. Response will be evaluated after every 2 cycles. Treatment will continue until disease progression based on RECIST criteria or intolerable toxicity. Subjects who voluntarily stop the study, have progressive disease, or unacceptable toxicities will be followed for survival every 2 months for 12 months from start of study treatment, then every 3 months for up to 24 months.

Correlative research analyses include examining the relationship between procaspase 3 expression in archived tumor tissue to degree of clinical response.

12.2 Criteria for Stopping Study

After the first 15 subjects are enrolled, the study will be stopped if 2 or more subjects develop treatment related grade 5 toxicity (death).

12.3 Sample Size and Accrual

Previous studies in the target population identified PFS at 3 months of 38%.[6] We hypothesize PFS at 3 months of 65%. Controlling for a probability of Type I error at 0.05 (one-sided), our sample size in Phase 2 is estimated to be 32 to ensure 90% statistical power in successfully detecting an alternative PFS rate at 3 months of 0.65, compared to a null rate of 0.38. With 3 additional patients to account for a 10% drop off rate, sample size for phase 2 study will be 35. Sample size analyses were conducted using the PASS software (NCSS, Kaysville, Utah, USA). With phase1b study component, the study will need to have 3 subjects from Dose Level 1 of Phase 1b + 6 subjects from Dose Level 2 of Phase 1b (and carried over to Phase 2 study). The total number of subjects for the study is 38.

12.3.1 Number of subjects to be enrolled

Number to be enrolled:

Phase 1b: minimum of 9, maximum of 12
Phase 2: 6 subjects from MTD level in Phase 1b and an additional 29 subjects for a projected sample size of 35.

12.4 Analysis Datasets

12.4.1 Evaluable for Safety

This will be comprised of all subjects who receive at least one dose of trial drug.

12.4.2 Evaluable for Efficacy

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.)

12.5 Data Analysis Plans

12.5.1 Analysis Plans for Primary Endpoint

Phase Ib Analysis of Primary Endpoint
The primary endpoint is determination of the MTD of PAC-1 in combination with entrectinib. The MTD will be defined as the highest explored dose of PAC-1 combined with 600 mg of entrectinib at which ≤1 out of 6 subjects have experienced a DLT within the first cycle of therapy. That dose will be recommended for the Phase 2 study (i.e., will be declared the RP2D). At the discretion of the sponsor-investigator, a lower Phase 2 dose may be recommended if other toxicity emerges during the Phase Ib study which does not meet DLT criteria but limits the dose that can be administered cumulatively.

Phase II Analysis of Primary Endpoint
The primary endpoint is determination of the activity of the combination of PAC-1 and entrectinib for treatment of metastatic uveal melanoma, as assessed by 3 months PFS based on RECIST v1.1. Median PFS times will be computed with associated 95% confidence intervals. Kaplan-Meier curves will be plotted.

12.5.2 Analysis Plans for Secondary Endpoints

12.5.2.1 Phase 1b Analysis of Secondary Endpoints

Safety and tolerability by NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5 on treatment with PAC-1 in combination with entrectinib in subjects with metastatic uveal melanoma.

Proportion of subjects with each grade of adverse events as defined by CTCAE v.5.0 will be computed along with 95% confidence intervals and reported in a tabular and descriptive manner.

PFS at 3 month in subjects with metastatic uveal melanoma treated with PAC-1 in combination with entrectinib.

PFS will be analyzed using the Kaplan-Meier method, and median PFS will be computed with associated 95% confidence interval. Subjects who have not progressed will be right-censored at the date of the last disease evaluation. Kaplan-Meier curves will be plotted. Data will be analyzed using the PROC LIFETEST in SAS.

ORR in subjects with metastatic uveal melanoma treated with PAC-1 in combination with entrectinib.

ORR will be estimated according to RECIST 1.1, by dividing the total number of responders (complete plus partial responses) by number of subjects with measurable disease and the exact 95% confidence interval will be computed.

DoR on treatment with PAC-1 in combination with entrectinib in subjects with metastatic uveal melanoma.

DoR will be evaluated for subjects who achieve CR or PR using the Kaplan-Meier method. For such patients, DoR is defined as the number of months from the start date of CR or PR (whichever response status is observed first) and subsequently confirmed, to the first date that recurrent or progression disease (PD) is objectively documented. If a subject dies, irrespective of cause, without documentation of recurrent or PD beforehand, then the subject's date of death will be used to denote the response end date. Subjects who have not progressed will be right-censored at the date of the last disease evaluation. Median DoR will be computed with associated 95% confidence interval, and Kaplan-Meier curves will be plotted.

OS of subjects with metastatic uveal melanoma treated with PAC-1 in combination with entrectinib.

OS will be analyzed using the Kaplan-Meier method, and median OS times will be computed with associated 95% confidence intervals. Subjects who have not died will be right-censored at the date of the last follow-up, and Kaplan-Meier curves will be plotted. Data will be analyzed using the PROC LIFETEST in SAS.

12.5.2.2 Phase 2 Analysis of Secondary Endpoints

Safety and tolerability by NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5 on treatment with PAC-1 in combination with entrectinib in subjects with metastatic uveal melanoma.

Proportion of subjects with each grade of adverse events as defined by CTCAE v.5.0 will be computed along with 95% confidence intervals, and reported in a tabular and descriptive manner.

ORR in subjects with metastatic uveal melanoma treated with PAC-1 in combination with entrectinib.

ORR will be estimated according to RECIST 1.1, by dividing the total number of responders (complete plus partial responses) by number of subjects with measurable disease and the exact 95% confidence interval will be computed.

DoR on treatment with PAC-1 in combination with entrectinib in patients with metastatic uveal melanoma.

DoR will be evaluated for subjects who achieve CR or PR using the Kaplan-Meier method. For such subjects, DoR is defined as the number of months from the start date of CR or PR (whichever response status is observed first) and subsequently confirmed, to the first date that recurrent or progression disease (PD) is objectively documented. If a subject dies, irrespective of cause, without documentation of recurrent or PD beforehand, then the subject's date of death will be used to denote the response end date. Subjects who have not progressed will be right-censored at the date of the last disease evaluation. Median DoR will be computed with associated 95% confidence interval, and Kaplan-Meier curves will be plotted.

OS of subjects with metastatic uveal melanoma treated with PAC-1 in combination with entrectinib.

OS will be analyzed using the Kaplan-Meier method, and median OS times will be computed with associated 95% confidence intervals. Subjects who have not died will be right-censored at the date of the last follow-up, and Kaplan-Meier curves will be plotted. Data will be analyzed using the PROC LIFETEST in SAS.

12.5.3 Analysis Plans for Correlative Objectives

Pharmacokinetic analyses of PAC-1 and entrectinib. Compare procaspase 3 expression in tumor tissue to degree of clinical response.

Tumor specimen either collected at diagnosis or obtained at enrollment will be submitted to Dr Tim Fan, University of Illinois and will be correlated with ORR assessed by imaging (revised RECIST 1.1 criteria). Spearman correlation will be computed using PROC CORR in SAS (Cary, NC).

12.5.4 Other Planned Analyses

Descriptive statistics will be provided to summarize demographics and baseline characteristics parameters. Categorical data will be summarized as frequency and its corresponding percentage. For continuous data, frequency (n), mean, standard deviation, median (as appropriate), minimum, and maximum will be provided for each of the parameters.

12.6 Interim Analysis/Criteria for Stopping Study

No interim analyses are planned for this study. However, the Data Safety Monitoring Board will be reviewing study safety and treatment activity periodically and provide recommendations regarding need for stopping study. See Section 13 for additional information.

13 TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

HCRN oversight activities include**:**

- Review and processing of all adverse events requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information and data summary reports to the sponsor-investigator
- Submit data summary reports to the DSMB for review according to DSMB Charter

This study will have a Data and Safety Monitoring Board (DSMB). The DSMB is chaired by an independent medical oncologist external to this trial. The DSMB will provide a recommendation to the sponsor-investigator after all information is reviewed. This information will also be provided to HCRN who will distribute to the site investigator/participating sites for submission to their respective IRB according to the local IRB's policies and procedures.

The DSMB review will include but is not limited to:

- Adverse event summary report
- Audit results if applicable
- Data related to stopping/decision rules described in study design
- Study accrual patterning
- Protocol deviations

The DSMB will meet twice annually during the active study drug administration phase. Additional DSMB meetings may be convened upon request of the Sponsor-Investigator, DSMB, or other applicable oversight body.

13.2 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

Participating sites may also be subject to quality assurance audits by Genentech and Vanquish Oncology, Inc. or their designees as well as inspection by appropriate regulatory agencies.

13.2.1 Onsite Monitoring

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. For cause visits may occur as necessary. Selected source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by HCRN or its designee.

The trial site may also be subject to quality assurance audit by Genentech/Roche and Vanquish Oncology, Inc. or their designees as well as inspection by appropriate regulatory agencies.

13.3 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to HCRN for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Management

HCRN will serve as the Clinical Research Organization for this trial. Data will be collected through a web based clinical research platform, a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality control assurance and integrity. Select data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submissions

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at a minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator and HCRN.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure and password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, Genentech and Vanquish Oncology, Inc., the IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

15 ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to HCRN before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.

Progress reports and notifications of serious and unexpected adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

16 REFERENCES

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APPENDIX 1: ECOG PERFORMANCE STATUS

ECOG Score	Performance Status
0	Asymptomatic
1	Symptomatic, fully ambulatory
2	Symptomatic, in bed < 50% of the day
3	Symptomatic, in bed > 50% of the day but not bedridden
4	Bedridden
5	Dead

APPENDIX 2: DRUG INTERACTIONS WITH ENTRECTINIB

Because of the potential for drug interactions, entrectinib should be administered with caution with the drugs listed in the tables below.

Cytochrome P450 CYP3A4 Inhibitors and Inducers

Inhibitors	Inducers
Strong: Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole Moderate: Aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil	Strong: Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, rifampin, St. John's Wort Moderate: Bosentan, efavirenz, etravirine, modafinil

Cytochrome P450 Substrates

	Sensitive Substrates	Substrates with Narrow Therapeutic Range
CYP2C9 Substrates	Celecoxib	Warfarin
CYP2D6 Substrates	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	Thioridazine, pimozide
CYP3A Substrates	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, ticagrelor, vardenafil	Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus