PROTOCOL TITLE: Lenvatinib in Recurrent Hepatocellular Carcinoma After Liver Transplantation

WINSHIP PROTOCOL #: Winship5381-21

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University of Alabama at Birmingham IRB needs to review the protocol

Name, Title(s), Institution, and Department of External Collaborators
(For each entry, please indicate whether that institution's IRB will review (or has already reviewed) that individual's engagement in human participants research activities)

VERSION: Version 7.0; 1/14/2025

FUNDING SOURCE: Eisai

INVESTIGATIONAL PRODUCT (IP): Lenvatinib, Eisai
OTHER AGENT(S): None

IND #: 157590

REVISION HISTORY

Revision #	Version Date	Summary of Changes
1	6/7/2022	PI Change, Staff updates on pages 1&2, change in lab on page 19, ctDNA to replace circulating tumor cells on pages 8, 19 & 20, updated section 11
2	6/10/2022	Enrollment number updated in version 6/7/2022 in error; enrollment number being updated back to the original 17
3	3/28/2023	Adding UAB as a multi-site, changing the lab address from Emory to UAB, adding UAB throughout document where applicable, changed enrollment numbers
4	03/04/2024	Change protocol and lab manual to specify Lesinski Laboratory is the site of blood sample collection on Page 18 and in Laboratory Manual
5.	03/28/2024	Update protocol schedule of activities to reflect change from even cycles Cycle 10 to Cycle 8- 24
6.	1/14/2025	Update to the schedule of assessments and removing Mayo as a site.

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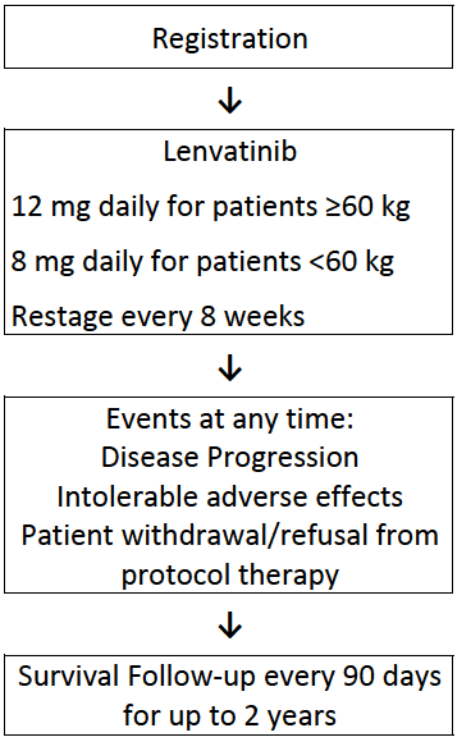
1. Study Summary

1.1 Synopsis

Title:	**Lenvatinib in recurrent hepatocellular carcinoma after liver transplantation**
Study Description:	This research study is an open label, single arm, Phase II study, designed to evaluate the safety and tolerability/efficacy of lenvatinib in subjects with recurrent hepatocellular carcinoma after liver transplantation. Patients with biopsy proven recurrent HCC after liver transplantation will be started on lenvatinib. Restaging scans will be performed every 8 weeks. Peripheral blood samples will be collected prior to treatment, on cycle 3 day 1, and at progression for correlative research. Treatment will be continued until progression, excessive toxicity, or patient withdrawal from protocol therapy.
Objectives:	**Primary Objective**: To evaluate the anti-tumor activity of lenvatinib by assessing the overall response rate (ORR) by RECIST version 1.1. **Secondary Objectives:** • To evaluate the safety and tolerability of lenvatinib in patients with recurrent HCC after liver transplantation • To evaluate the anti-tumor activity of lenvatinib by assessing progression free survival (PFS) and overall survival (OS) and duration of response. **Exploratory Objective:** • To evaluate the effect of treatment on selected biomarkers in systemic circulation.
Endpoints:	**Primary Endpoint:** • Efficacy ORR (Complete response +partial response) per RECIST version 1.1 **Secondary Endpoints:** • Safety: adverse events, vital sign measurements, physical examinations, and clinical laboratory test. • Efficacy: Progression free survival (PFS) and overall survival (OS), duration of response • Exploratory: Changes in selected biomarkers in circulation before and after treatment with lenvatinib.
Study Population:	• The patient population consists subjects ≥18 years of age with biopsy proven recurrent HCC after liver transplantation. Eligible patients must have/have not received any systemic therapy for HCC in the post-transplant setting.
Phase:	II

Description of Sites/Facilities Enrolling Participants:	Winship Cancer Institute of Emory University (Atlanta, GA). Mayo Clinic Arizona (Arizona) Mayo Clinic Rochester (Minnesota) University of Alabama at Birmingham (Birmingham, AL)
Description of Study Intervention:	Patients will receive the following treatment: Lenvatinib 12 mg daily for patients ≥60 kg, 8 mg daily for patients <60 kg. Study drugs will be given PO on Days 1-28. Treatment cycles are 28 days.
Study Duration:	Patients will be treated until unacceptable toxicity, patient withdrawal from protocol therapy or disease progression per Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST v1.1).

1.2 Schema



Cycle = 28 days
Treatment until progression, excessive toxicity, or patient withdrawal from protocol therapy.
Survival follow-up, every 90 days until death or 2 years from registration.

1.3 Schedule of Assessment

While patients are receiving treatment (up to 24 cycles), please use the following Table 1:

	Screening	Active monitoring phase													
Procedures	**Day -28 to -1**	**Cycle 1 Day 1**	**Cycle 1 Day 7**	**Cycle 1 Day 14**	**Cycle 2 Day 1**	**Cycle 2 Day 14**	**Cycle 3 Day 1**	**Cycle 4 Day 1**	**Cycle 5 Day 1**	**Cycle 6 Day 1**	**Odd cycles 7-23 Day 1**	**Even cycles 8-24 Day 1**	**End of treatment**	**Safety follow up**	**Long term follow up every 90 days (+/-14 days)**
Informed consent[1]	X														
Demographics	X														
Medical history	X														
Administer study intervention		X	X	X	X	X	X	X	X	X	X	X			
Con. medication review	X	X	X----------										X		
Physical exam (including height and weight)[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology [4]	X	X		X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry [5]	X	X		X	X	X	X	X	X	X	X	X	X	X	
Urine analysis	X				X		X	X	X	X	X	X			
TSH, Free T4 and T3	X				X			X		X		X			
AFP	X	X			X		X	X	X	X	X	X	X		
Coagulation studies (PT, INR, aPTT)	X														
Hepatitis and HIV screening[6]	X														
Pregnancy test[7]	X	X			X		X	X	X	X	X	X	X	X	
EKG [8]	X														
AEs review and evaluation	X	X	X----------										X		X
Survival status														X	X
Radiologic/Imaging assessment[9]	X				X[9]			X[9]		X[9]		X			
Other assessments (Correlative blood samples)[10]		X					X						X		
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[1] If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of Cycle 1 Day 1.

[2] Height only at screening

[3] Blood pressure should be monitored after 1 week of treatment with lenvatinib, then every 2 weeks for the first 2 months and monthly thereafter while on treatment. If a patient develops systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg active management is indicated.

[4] CBC with differential. If screening hematology assessment performed within 3 days prior to day 1, they do not need to be repeated on day 1.

[5] Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium. If screening clinical chemistry assessment performed within 3 days prior to day 1, they do not need to be repeated on day

[6] Hepatitis B surface antigen, Hepatitis C antibodies, HIV antibodies

[7] For women of childbearing potential only. Urine pregnancy test with positive verified via blood serum pregnancy test. Women of childbearing potential are required to have a serum or urine pregnancy test within 72 hours prior to the first dose of study drug and then every 4 weeks. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion

[8] Any clinically significant abnormalities detected require triplicate ECG results obtained over a brief period (within 30 minutes) to confirm the finding

[9] Imaging will be evaluated for radiographic response using RECIST v1.1 on images from CT or MRI, each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands) and pelvis. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Imaging will be performed at 8 weeks (+/-7 days) of initiation of protocol treatment, and repeated every 8 weeks (+/-7 days). Same imaging modality utilized in the screening should be performed in subsequent scans unless deemed not suitable or safe by the principal investigator.

[10] Blood for correlative studies will be collected at baseline prior to systemic therapy, on cycle 3 day 1, and at off protocol treatment

2. Objectives (and Endpoints)

OBJECTIVES	ENDPOINTS
Primary	
3. To evaluate anti-tumor activity of the lenvatinib by assessing the overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST v1.1).	• Efficacy: • ORR per RECIST v1.1 (Tumor measurements will be performed every 8 weeks ± 7 days
Secondary	
• To evaluate the safety and tolerability of lenvatinib in patients with recurrent HCC after liver transplantation. • To evaluate the anti-tumor activity of the lenvatinib by assessing progression-free survival (PFS) and overall survival (OS) and duration of response	• Safety: adverse events, vital sign, ECG, physical examinations, clinical laboratory test. • Progression-free Survival (PFS) using RECIST 1.1 • Overall Survival • Duration of response
Tertiary/Exploratory	
• To assess the effects of the lenvatinib on circulating tumor DNA and biomarkers	• Changes in circulating tumor DNA and biomarkers after treatment lenvatinib and their relationship with efficacy.

3. Background

Hepatocellular carcinoma (HCC) is the second leading cause of cancer related mortality in the world.(1) HCC is the fastest increasing cause of cancer-related mortality in the US and 5 year survival is less than 12%.(2) About 40% of patients with HCC can be candidates for curative treatments (ablation, surgical resection, liver transplantation)(3) but most present at advanced stage. Liver transplantation is a curative option in hepatocellular carcinoma with 5 years overall survival between 65%-85%.(4) However, up to 20% of patients develop recurrent disease in 5 years and prognosis remains poor.(4-6) HCC recurrence post-transplant is usually extrahepatic (up to 67%) hence requires effective systemic therapy options.(6, 7) Recurrent HCC after transplantation is defined as metastasis from the native liver that could occur due to undetected extrahepatic metastasis that was present before liver transplantation or due to circulating HCC cell clones engrafting into target organ.(5, 6) Current FDA-approved systemic treatment options in advanced HCC include sorafenib, lenvatinib, atezolizumab/bevacizumab in the first line setting, regorafenib, cabozantinib, nivolumab, pembrolizumab, ramucirumab, nivolumab/ipilimumab in the second line setting.(8-14) **None of these agents were studied in patients with prior liver transplantation therefore systemic therapy is not established in patients with recurrent HCC after liver transplantation.** Although systemic treatment of advanced HCC has several options, management of patients with recurrent HCC after liver transplantation poses a unique challenge

for routine clinical practice due to the absence of clear guidance from international guidelines. Lack of prospective clinical trial data and limited data from retrospective case series indicates an area of unmet need in treatment of recurrent HCC post liver transplantation. Lack of prospective clinical trial data to support recommendations in international guidelines can create challenges to acquire newly approved systemic therapy agents in this special subgroup of HCC patients in the clinical practice.(15)

3.1 Study Rationale

The data for systemic therapy agents in recurrent HCC post-transplant is limited to retrospective case series.(5, 16) Since sorafenib was the only approved systemic therapy agent in advanced HCC for almost a decade majority of the data is limited to retrospective studies with sorafenib in post-transplant HCC.(5, 17-19) In a systematic review of literature including 1,021 patients with recurrent HCC after liver transplantation sorafenib was utilized in 20% of patients, 42.1% of the patients required dose reductions, 46.5% achieved stable disease.(6) Regorafenib was studied in 28 patients who progressed on sorafenib in recurrent HCC post-transplant setting and revealed median OS of 12.9 months.(20) Despite these retrospective data with sorafenib and regorafenib, both agents have been associated with increased toxicities when combined with immunosuppression in post-transplant recurrent HCC.(18, 20) Regorafenib was associated with increased plasma levels of immunosuppressant agents in a retrospective study (20) and sorafenib was associated with frequent dose reductions and discontinuation due to adverse events in other retrospective studies in post-transplant setting.(17) As more novel and better tolerated agents emerge in advanced HCC treatment it is warranted to explore these agents in recurrent HCC after liver transplantation in a prospective manner.

There are no evidence-based recommendations from international guidelines in regard to systemic therapy in this unique subpopulation of HCC. Given tolerability and efficacy of lenvatinib in advanced HCC and encouraging data from respective reports in recurrent HCC after liver transplant we propose a prospective multicenter (Emory, UAB and Mayo Clinic) phase II study with single agent lenvatinib in recurrent HCC after liver transplantation.

3.2 Clinical Experience

Lenvatinib is a multikinase inhibitor targeting VEGFR1-3, FGFR1-4, KIT, PDGFRα, and RET selectively hence plays a significant role in anti-angiogenesis as well as direct inhibition of tumor cell proliferation.(21) In randomized non-inferiority phase III REFLECT trial lenvatinib was non-inferior to sorafenib in first line treatment of unresectable HCC.(11) Based on results of this trial on August 16th, 2018 the FDA approved lenvatinib for the first-line treatment of patients with unresectable HCC. In REFLECT trial 954 eligible patients with unresectable HCC were randomized to lenvatinib (12 mg [baseline body weight ≥60 kg] or 8 mg [baseline body weight <60 kg]) given orally once daily or sorafenib 400 mg given orally twice daily. Patients were required to have a histologically or cytologically confirmed diagnosis of advanced HCC, or a clinically confirmed diagnosis of HCC according to the American Association for the Study of Liver Diseases criteria, including cirrhosis of any etiology, or with chronic hepatitis B or C infection. Patients had at least 1 measurable target hepatic or nonhepatic lesion according to mRECIST, and adequate liver, bone marrow, blood coagulation, renal, and pancreatic function. Patients were stratified by region, presence or absence of macroscopic portal vein invasion or extrahepatic spread or both, ECOG PS 0 or 1, and body weight (<60 kg or ≥60 kg). The majority of patients in both treatment arms had an ECOG PS of 0 at Baseline (63%), Child-Pugh score of 5 (76%), and weighed ≥60 kg (69%). The median age was 62 years, 84% were male, 16% were female, 69% were Asian, 1% were black, and 29% were white. Lenvatinib was noninferior for OS to sorafenib 400 mg twice daily. Median OS was 13.6 months compared to 12.3 months for sorafenib with HR = 0.92 [95% CI (0.79, 1.06)]. Based on investigator assessment evaluated according to mRECIST, lenvatinib treatment resulted in statistically significant (P<0.00001) and clinically meaningful improvement over sorafenib in the secondary endpoints of PFS and ORR. Lenvatinib treatment significantly prolonged TTP compared to sorafenib, with a median TTP that was more than twice as long as that of sorafenib. Retrospective independent

review of imaging corroborated the secondary endpoints of PFS, TTP and ORR. Objective response rate was 24.1% vs 9.2%, respectively by mRECIST and 18.8% and 6.5% by RECIST version 1.1. Patients with prior organ transplantation were excluded in the REFLECT trial limiting applicability of lenvatinib in this special subgroup of HCC patients. Yang et al. evaluated the efficacy of various treatments for recurrent HCC after liver transplantation in a Chinese patient population. Of the 64 patients with recurrent HCC after LT. Median OS in sorafenib-tolerant patients treated with Lenvatinib was 19.5 months, significantly exceeding the patients that discontinued sorafenib or were treated with regorafenib after sorafenib failure.(7) Despite limited retrospective data with different tyrosine kinase inhibitors with various success rates in mostly single center studies there is no prospective data on safety and efficacy of lenvatinib in recurrent HCC after liver transplantation.

4. Study Intervention/Investigational Agent

4.1 Description

Lenvatinib 4-[3-Chloro-4-(*N*'-cyclopropylureido)phenoxyl]- 7-methoxyquinoline- 6-carboxamide methanesulfonate (lenvatinib mesilate) is an oral, potent multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors (VEGFRs), VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other pro-angiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors (FGFRs)1-4, platelet-derived growth factor receptor (PDGFR)α, KIT, and RET. Nonclinical studies showed lenvatinib to be a potent antiangiogenesis agent with antitumor activity versus various human cancer xenograft models in athymic mice and murine tumor isograft models in immunocompetent mice. Lenvatinib drug substance is a white to pale yellow powder that is being used in the capsule formulation for the clinical studies evaluating lenvatinib. It is slightly soluble in water and has a molecular weight of 522.96 and a pKa of 5.27 (mesilate salt).

4.2 Drug/Device Handling

Lenvatinib capsules are packaged in cold form blisters or high-density polyethylene bottles with a polypropylene cap and desiccant. The blisters and bottles should be stored under room temperature. The recommended daily dose of lenvatinib is 8 mg (two 4 mg capsules) once daily for patients with a body weight of <60 kg and 12 mg (three 4 mg capsules) once daily for patients with a body weight of ≥60 kg (Table 2). The daily dose is to be modified, as needed, according to the dose/toxicity management plan (Table 3).

4.3 Accountability

The study drug provided for this study will be used only as directed in the study protocol. The IDS (Investigational Drug Service) personnel at Winship, UAB and Mayo Clinics will account for all study drugs. Drug accountability should be performed until the patient stops study treatment completely. Study site personnel will account for all study drugs received at the site.

Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels. The Investigator, pharmacist, or designee must maintain an accurate record of dispensing the study drug/s in a Drug Accountability Log.

The Drug Accountability Log may record specifics to study drug dispensation such as:

• Records of product delivery, inventory, temperature monitoring, destruction, and return.

• Dosages prepared, time prepared, doses dispensed.
• Doses and/or vials destroyed.
• The Drug Accountability Log may be reviewed by the monitor during site visits and at the completion of the study.

Drug accountability may be noted by the internal monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.
The study drug supply will be disposed of per institutional' s Investigational Drug Service (IDS) SOP.

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver (collection of drug diary and pill counts) will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.
The patient might be requested to maintain a medication diary of each dose of medication. The medication diary (Appendix B) will be returned to clinic staff at the end of each cycle.
Dose changes and interruptions of study drug must be specifically documented in the patient source documents and eCRF.

5. Procedures Involved

5.1 Study Design

This clinical trial is a Phase II study, designed to evaluate the safety and tolerability/efficacy of lenvatinib in subjects with recurrent hepatocellular carcinoma after liver transplantation.

The study is divided into a Screening period, Treatment period, End of Treatment (EOT) period, and Follow-up period.

During the Screening period patients will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the patient's standard care. Procedures that were performed for standard of care prior to signing informed consent may be used for screening purposes (e.g., full physical exam) as long as the procedures were completed within the **28-day screening period**. After signing the ICF, patients will be evaluated for entry criteria during the screening period within 28 days before administration of study drug(s). Rescreening after screen failure will be allowed.

Treatment will continue until unacceptable toxicity, death, disease progression per RECIST 1.1, Investigator's decision to discontinue treatment, the patient withdraws consent, is lost to follow-up, or Institution decides to terminate the trial.
Patients with PD per RECIST 1.1 but with otherwise stable or improved performance and clinical status may continue to be treated in the event of a perceived benefit per Investigator; see Section "Treatment beyond progression". Investigators have to discuss with site PI prior to continuing treatment beyond progression. Patients with a PR or SD will continue to receive treatment until achievement of a confirmed complete response (CR), disease progression, or intolerability to therapy. It is at the discretion of the Investigator to continue treating patients with a confirmed CR.

5.2 Dosing and Administration

Initial dose regimen

The recommended daily dose of lenvatinib is 8 mg (two 4 mg capsules) once daily for patients with a body weight of <60 kg and 12 mg (three 4 mg capsules) once daily for patients with a body weight of ≥60 kg. The daily dose is to be modified, as needed, according to the dose/toxicity management plan.

The treatment to be used in this trial is outlined below in **Table 2**

Table 2: Trial Treatment

Drug	Dose/Potency	Dose Frequency	Cycles	Route of Administration
Lenvatinib	**≥60 kg BW 12 mg (three 4 mg Capsules)**	Once daily	ALL	oral
	<60 kg BW 8mg (two 4 mg Capsules)	Once daily	ALL	oral

5.3 Definition of Dose-Limiting Toxicity

N/A

5.4 Dose Modification

The investigator will decide whether any AE that occurs is related to study drug and determine whether dose modification or discontinuation of study drug is required per the guidance below. Management of some adverse reactions may require dose interruption, adjustment, or discontinuation of lenvatinib therapy. Mild to moderate adverse reactions (eg, Grade 1 or 2) generally do not warrant interruption of lenvatinib, unless intolerable to the patient despite optimal management.

Reduce dose, withhold dose, or discontinue STUDY DRUG to manage adverse reactions as described in Table 3 below and are based on criteria in the package insert.

Table 3: Dose Modification for Adverse Events Associated with Lenvatinib

Starting Dose		**≥60 kg BW 12 mg (three 4 mg capsules orally once daily)**	**<60 kg BW 8mg (two 4 mg capsules orally once daily)**
Persistent and Intolerable Grade 2 or Grade 3 Toxicities [a]			
Adverse Reaction	**Modification**	**Adjusted Dose[b] (≥60 kg BW)**	**Adjusted Dose[b] (<60 kg BW)**

First occurrence [c]	Interrupt until resolved to Grade 0-1 or baseline[d]	8 mg (two 4 mg capsules) orally once daily	4 mg (one 4 mg capsule) orally once daily
Second occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline[d]	4 mg (one 4 mg capsule) orally every day	4 mg (one 4 mg capsule) orally every other day
Third occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline [d]	4 mg (one 4 mg capsule) orally every other day	Discontinue
Life-threatening toxicities (Grade 4): Discontinue [e]			
[a] Initiate medical management for nausea, vomiting, or diarrhea prior to interruption or dose reduction [b] Reduce dose in succession based on the previous dose level (12 mg, 8 mg, 4 mg or 4 mg every other day) [c] Hematologic toxicity or proteinuria - no dose adjustment required for first occurrence [d] For hematologic toxicity or proteinuria can restart when resolved to Grade 2 [e] Excluding laboratory abnormalities judged to be non life-threatening, which should be managed as Grade 3			

Patients with Hypertension

Blood pressure should be well controlled prior to treatment with lenvatinib and should be regularly monitored during treatment. When necessary, manage hypertension as recommended in Table 4 below:

Table 4: Recommended Management of Hypertension

Blood Pressure Level	Recommended Action
Systolic BP ≥140 mmHg up to 160 mmHg or diastolic BP ≥90 mmHg up to 100 mmHg	Continue lenvatinib and initiate antihypertensive therapy, if not already receiving OR Continue lenvatinib and increase the dose of the current antihypertensive therapy or initiate additional antihypertensive therapy
Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg despite optimal antihypertensive therapy	Withhold lenvatinib When systolic BP ≤150 mmHg, diastolic BP ≤95 mmHg, and patient has been on a stable dose of antihypertensive therapy for at least 48 hours, resume lenvatinib at a reduced dose
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management

BP=Blood pressure

5.5 Concomitant medication

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.

Acceptable Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded. In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrhea) and safety of the patient are allowed.

• Medications to prevent or treat nausea or vomiting. • Anti-diarrheal medications (e.g., loperamide) for patients who develop diarrhea. • Pain medication to allow the patient to be as comfortable as possible. • Treatment with bisphosphonates or denosumab for pre-existing, painful bone/liver metastases, and limited-field palliative radiotherapy or surgery is permitted. Patients requiring initiation of such treatment during the course of the study must be evaluated for disease progression; radiotherapy like any concomitant medication must be listed on the CRF.

• Hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF), thrombopoietin mimetics or erythroid stimulating agents as per local or published guidelines; in case of anemia, thrombocytopenia or neutropenia, potential immune mediated etiology should be ruled out • Nutritional support or appetite stimulants (e.g. megestrol). • Oxygen therapy and blood products or transfusions. • Inactivated vaccines. • The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications

Prohibited concomitant medications

During the course of the study, patients must not receive other antineoplastic therapies (e.g. investigational drugs, devices, chemotherapy, immunotherapies). However, limited-field palliative radiotherapy may be allowed as concomitant therapy (see above). The use of live vaccines is not allowed through the whole duration of the study. Inactivated vaccines are allowed. There are no prohibited therapies during the post-treatment follow-up period.

Rescue Medications & Supportive Care

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once every 2 weeks (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as

ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary. All patients must be followed up for adverse events and serious adverse events until start of new antineoplastic medication for 28 days after discontinuation of study drugs, whichever is sooner.
Suspected SAEs will continue to be collected beyond the 150-Day safety visit. This will be done by return clinic visits, laboratory checks, and phone calls

5.6 Study Procedures

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate **safety and tolerability assessments**. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided following the Protocol Synopsis.

Screening Phase

Screening procedures will be performed up to 28 days prior to initiation of protocol therapy as applicable. All subjects must first read, understand, and sign the IRB-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the screening window.
The following procedures will be performed during the **Screening Visit**:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- 12-lead ECG
- Review of prior/concomitant medications
- Imaging by CT/MRI (within 28 days)
- Clinical laboratory tests for:
  - Hematology
  - Clinical chemistry
  - TSH, free T4, T3
  - Coagulation (PT, INR, aPTT)
  - Creatinine or Creatinine Clearance
  - Serum or urine pregnancy test (for women of childbearing potential)
  - Hepatitis B surface antigen, Hepatitis C antibodies, HIV antibodies
  - Urinalysis
  - Alpha fetoprotein (AFP)

Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments (Section 1.3). Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

- Brief medical history
- Symptom-directed physical exam
- ECOG Performance Status
- Vitals signs, weight
- Review of prior/concomitant medications
- Clinical laboratory tests for:
  - Hematology
  - Clinical chemistry
  - TSH, Free T4 and T3
  - AFP
  - Serum or urine pregnancy test (for women of childbearing potential)
  - Urinalysis (see Urine analysis tests)

Drug Treatment description

Drug	Dose/Potency	Dose Frequency	Cycles	Route of Administration
Lenvatinib	**≥60 kg BW 12 mg (three 4 mg capsules**	Once daily	ALL	oral
	<60 kg BW 8mg (two 4 mg capsules	Once daily	ALL	oral

End of Treatment

- End of treatment is defined as the last planned dosing visit within the dosing period. For subjects who discontinue drug treatment, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within **± 7 days** of the end of treatment visit. Repeat disease assessment is not required if performed within **28** days prior to the end of treatment visit.
- Assessments for subjects who have completed treatment and achieved disease control or have discontinued treatment due to toxicity in the absence of confirmed progressive disease are provided in the Schedule of Events.
- All subjects will be followed for survival until the end of the study regardless of further treatments, or until the sponsor ends the study.

5.7 Description of Study Procedures

Medical history

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examination

Physical examinations should be conducted according to the Schedule of Events. Full physical examinations should be conducted at screening/baseline, Day 1 of cycle 2 and beyond, and EOT (evaluate all major organ systems, including the following categories: general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic, and psychiatric). Other examinations may be focused, at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the patient's clinical symptoms. Weight is to be recorded at each visit, height at screening/baseline visit only.

Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules. Body weight is also recorded along with vital signs.
The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.
At Screening, a single ECG will be obtained on which QTcF must be ≤480 ms.
In case of clinically significant ECG abnormalities, including a QTcF value >480 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.
The Investigator or qualified Sub-Investigator will review all ECG interpretations and interval duration measurements for clinical significance. Any ECG interpretation deemed to be clinically significant will be reported as an AE.

Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments)

- Hematology and Clinical Chemistry
- Urinalysis
- Coagulation parameters: Activated partial thromboplastin time and International normalized ratio to be assessed at baseline and as clinically indicated
- Pregnancy test (female subjects of childbearing potential only)
  - Serum or Urine human chorionic gonadotropin
- Thyroid Stimulating Hormone
  - TSH, Free T3 and free T4
- Other laboratory tests
  - Hepatitis B surface antigen, hepatitis C antibody
  - HIV antibody

Hematology Laboratory Tests

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count
Mean corpuscular hemoglobin concentration	

Clinical chemistry (serum or plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase
Amylase	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase	Uric acid

[a] If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin

Urinalysis Tests

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

5.8 Tumor and Radiographic Assessments

Tumor assessments for all patients will be performed at Screening and after 8 weeks (± 7 days) of protocol treatment. Assessments will be performed every 8 weeks during the long-term follow-up period. Tumor response will be evaluated using RECIST v1.1. (Appendix C)
Radiographic assessments (chest/abdomen/pelvis, and other known affected anatomical areas) are required for all patients for tumor measurements. Additional scan assessments may be collected based on clinical symptoms, as appropriate. Documented tumor measurements are required using CT scans, MRI, physical examination, and/or digital photography, as appropriate. Any imaging used to assess disease at any time point will be submitted for an independent radiology review. The same method of assessment (CT or MRI and/or digital photography) and the same technique for acquisition of images must be used for all study assessments (contrast must be used unless medically contraindicated). Baseline imaging should be done at the same institution/facility which will be used to measure response during the patient's participation in the study. Radiographic assessments and efficacy analyses will be conducted by the Investigator site.

5.9 Correlative Studies

Pre and post treatment peripheral blood for correlative studies including circulating tumor DNA (all patients), and biomarker analysis. Peripheral blood will be collected at baseline, on cycle 3 day 1 and at progression. Approximately 20 mL tubes of blood will be obtained for correlative studies at each of these time points. Blood samples will be collected, processed, stored and shipped to **Lesinski Lab** as per lab manual.

Lesinski Laboratory
Suite C3054, Bay 17
1365-C Clifton Rd. NE
Winship Cancer Institute of Emory University
Atlanta, GA 30322

6. Data and Specimen Banking

Blood samples will be obtained and used for medical research by the investigators of this study. *Data and specimens from this study may be useful for other research being done by investigators at Emory or elsewhere. To help further science, Investigators may provide de-identified data and/or specimens to other researchers. Any information that could identify participants will not be included. If data or specimens are labeled with study ID, we will not allow other investigators to link that ID to identifiable information.*

Samples and data collected under this protocol may be used to study **HCC**. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

The results of some study tests and procedures will be used only for research purposes and will not be placed in subject's medical record. For this study, those items include research blood collection.

Correlative peripheral blood samples will be collected prior to study drug allotment, prior to treatment on cycle 3 day 1, and at progression to assess effects lenvatinib on circulating tumor DNA.

7. Sharing of Results with Participants

In general, study staff will not provide any individual results to subjects (ex. outcome trial results or results from subject's samples studies). If something of urgent medical importance to the participating subjects will be found, the PI (or co-Is) will inform the subject, although we expect that this will be a very rare occurrence. Samples and data will only be used for research.

8. Study Timelines

8.1 Duration of therapy

In the absence of treatment delays due to adverse event(s), patients will be treated until any one of the following:

- Tumor progression per RECIST 1.1
- Death
- Unacceptable toxicity
- Symptomatic deterioration
- Achievement of maximal response
- Investigator's decision to discontinue treatment
- Patient decision to discontinue treatment
- Patient withdraws consent
- Lost to follow up

Sponsor or Eiasi terminate the study

In the event of a patient's withdrawal, the Investigator will make every effort to complete the End of Treatment procedures specified in the Schedule of Events.

Treatment Beyond Progression

Patients will be permitted to continue on treatment beyond initial RECIST 1.1-defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit and without rapid disease progression.
- Continue to meet all other study protocol eligibility criteria.
- Patient tolerates study drug(s).
- Patient has stable ECOG performance status of 0 or 1.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., central nervous system metastases). The assessment of clinical benefit should take into account whether the patient is clinically deteriorating and unlikely to receive further benefit from continued treatment.

All decisions to continue treatment beyond initial progression must be discussed with the site Principal Investigator and an assessment of the risk/benefit of continuing with study drug(s) must be documented in the study records. For patients who stay on treatment beyond RECIST 1.1-defined PD, all study procedures should

continue to be performed, including radiographic assessment by computed tomography (CT) (preferred) or magnetic resonance imaging (MRI).
Patients will be discontinued from treatment upon further evidence of disease progression, defined as an additional 10% or greater increase in the total tumor burden from the time of initial disease progression. The total tumor burden is calculated as the sum of the longest diameters (SLD) of all target tumors and SLD of all new measurable lesions. A new lesion is measurable if the longest diameter is at least 10 mm. Any new lesions that are non-measurable at the time of initial appearance and become measurable later will be included in the calculation of total tumor burden. The total tumor burden from the time of initial RECIST 1.1-defined progression will be used as the reference baseline for comparison with all post-progression assessments

8.2 Duration of follow-up

Patients will be followed for approximately 30 days **(Safety Follow-up)** after the last dose of study drug or before initiation of new antineoplastic or investigational therapy whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.
Long-term follow-up should continue until the patient's withdrawal of consent or loss to follow up, death, or study termination.

Patients in long term follow-up can be seen by medical oncology, have chart reviewed, or phone call to determine current status every 12 weeks (+/- 14 days) as indicated in the Section 1.3 Schedule of Assessments.

A participant will be considered **lost to follow-up** if he fails to return for three scheduled visits and is unable to be contacted by the study site staff after three attempts at contact by phone.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

Should the participant continue to be unreachable, he will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

Discontinuation from **study intervention** does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).
Patients may choose to discontinue the trial at any time, for any reason, and without prejudice to further treatment. The EOT visit will occur **30** days after the last dose of the study drug or before a new antineoplastic regimen has been initiated for patients enrolled.

The data to be collected at the EOT visit will include the following:

Vital signs, performance status, weight, physical exam, pregnancy test, hematology and clinical chemistry, thyroid function panel, urinalysis, and assessment of adverse events.

Replacement of Subjects

Subjects who sign the informed consent form and are assigned but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are assigned and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

9. Inclusion and Exclusion Criteria

A subject must fully meet all of the following criteria to be eligible for the study:

Inclusion Criteria

1. Male or Female
2. Age ≥18 years.
3. ECOG performance status ≤1 (Karnofsky ≥60%, see Appendix A).
4. Patients must have recurrent histologically or cytologically confirmed hepatocellular carcinoma that has recurred after liver transplantation and not amenable for surgical resection.
5. Child Pugh Class A
6. Prior orthotropic liver transplantation for curative intent
7. Measurable disease per RECIST version 1.1
8. Life expectancy > 12 weeks as determined by the Investigator
9. Patients must have adequate organ and marrow function, within 28 days of Cycle 1 Day 1, as defined below:

Hematology	
Hemoglobin	≥ 8.0 g/dl
Absolute neutrophil count (ANC)	≥ 1,500/mcL (after at least 7 days without growth factor support or transfusion)
Platelets	≥ 75,000/mcL
Coagulation	
International Normalized Ratio (INR)	≤2.3
Chemistry	
Total bilirubin	≤3 times the institutional upper limit of normal (ULN)
AST/ALT	≤ 5.0 times the ULN.
Albumin	≥2.8 g/dL
Serum creatinine	≤ 1.5× ULN or creatinine clearance ≥60 mL/min/1.73 m^2 for patients with creatinine levels >1.5 x ULN. Creatinine clearance should be calculated per institutional standard
Urinary protein	≤1+ on dipstick or routine urinalysis or 24-hour urine demonstrating <1 gram of protein

10. The effects of *lenvatinib* on the developing human fetus are unknown. For this reason female of child-bearing potential (FCBP) must have a negative serum or urine pregnancy test 72 hours prior to starting protocol therapy.
    Note: Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.
    Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
    - Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.

Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago

11. FCBP and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study treatment, and for 60 days after the last dose of protocol therapy. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study or for 60 days after the last dose of protocol therapy, she should inform the principal investigator immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 60 days after last dose of protocol therapy.
12. Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.
13. Willingness and ability of the subject to comply with scheduled visits, drug administration plan, protocol-specified laboratory tests, other study procedures, and study restrictions.
14. Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential risks and discomforts, potential benefits, and other pertinent aspects of study participation.

Exclusion criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Prior systemic therapy with lenvatinib or another FDA approved systemic therapy for hepatocellular carcinoma in the post-transplant setting.
2. Prior liver directed therapy is allowed, should be at least >28 days prior to the study enrollment. Should have at least one measurable untreated lesion by RECIST 1.1
3. Patients who have had radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier (*i.e.*, have residual toxicities > Grade 1).
4. Patients who are receiving any other investigational agents or an investigational device within 21 days before administration of first dose of study drugs.
5. History of allergic reactions attributed to compounds of similar chemical or biologic composition to

lenvatinib.

6. Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.
7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. Subjects with active hepatitis virus infection controlled with antiviral therapy are eligible.
8. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or stroke within 6 months of the first dose of study drug, or cardiac arrhythmia requiring medical treatment at Screening.
9. QTc interval >480 ms.
10. Uncontrolled blood pressure (Systolic BP>140 mmHg or diastolic BP >90 mmHg) in spite of an optimized regimen of antihypertensive medication.
11. Bleeding or thrombotic disorders or subjects at risk for severe hemorrhage. The degree of tumor invasion/infiltration of major blood vessels (e.g. carotid artery) should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy.
12. Subjects having > 1+ proteinuria on urine dipstick testing unless a 24-hour urine collection for quantitative assessment indicates that the urine protein is <1 g/24 hours.
13. Subjects who have not recovered adequately from any toxicity from other anti- cancer treatment regimens and/or complications from major surgery prior to starting therapy. Withhold lenvatinib for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing.
14. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] (or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or hCG]).
15. Females of child-bearing potential must be willing to use effective contraception during study and for 60 days after the last dose.
16. The participant has severe hypersensitivity (≥Grade 3) to lenvatinib and/or any of its excipients.
17. Patients with known HIV infection.
18. Participant with diagnosis, detection, or treatment of another type of cancer ≤2 years prior to initiating protocol therapy (except basal or squamous cell carcinoma of the skin and cervical cancer that has been definitively treated)

10. Vulnerable Populations

N/A

11.Local Number of Participants

We plan to have 17 participants complete the protocol required research procedures and estimate to enroll 26 participants across all sites in order to account for screen failures.

Emory: The number of participants who are expected to be enrolled and screened at Winship is 12, and the number of participants needed to complete the research procedures (i.e., numbers of participants excluding screen failures) is 8.

Mayo Clinic: The number of participants who are expected to be enrolled and screened at Mayo Clinic is 6, and the number of participants needed to complete the research procedures (i.e., numbers of participants excluding screen failures.) is 4.

UAB: The number of participants who are expected to be enrolled and screened at UAB is 8, and the number of participants needed to complete the research procedures (i.e., numbers of participants excluding screen failures.) is 5.

12.Recruitment Methods

Investigators, nurses, and/or data managers review lists of cancer patients who have cancer and will determine if there are patients who might be eligible for a clinical trial. The nurse/data manager reviews accessible medical records to screen further for eligibility. The nurse reviews the eligibility with the physician.
Subjects will be identified by their treating physicians. Clinical care team at Winship will inform potential subjects about the known benefits and potential risks of a clinical trial as well as other available treatment options.
Some of the subjects recruited for this protocol will be patients being treated at Emory and under the care of one or more of the study investigators. Some potential subjects will be identified by their treating physician and referred to Emory for possible participation in the protocol.
No incentives are provided to patients for trial participation.

Study personnel will notify Winship Central Subject Registration (WCSR) by email at winshipcsr@emory.edu, once subject has been consented for a trial.
Email notification must be done within 24 hours after consent has been obtained and it will include scanned copies of:

- Signed patient consent form
- HIPAA authorization form
- Emory Research Management System (ERMS; *https://erms.emory.edu*) Enrollment Fax Cover

The WCSR will enter the subject into the OnCore Research Management System, which is the system of record for Winship Cancer Institute Clinical Trials.

Participating Site (s)
A site- specific Central Subject Registration (CSR) form will be provided to each Participating Site.

After each subject signs consent, the Central Subject Registration form is to be completed and sent to Winship within 24 hours of consent. This form, along with the valid, signed informed consent form/HIPAA authorization form, is to be faxed or emailed to Winship's Central Subject Registrar per instructions on the form. Once a subject is registered, each participating site will be notified via e-mail.

Enrolling a subject requires careful screening and determination of eligibility.
Subjects who are consented to participate in the clinical trial, who do not meet one or more criteria required for participation in the trial during the screening procedures, will not be enrolled into the study and are considered **screen failures**. All subjects which have signed informed consent, and were deemed ineligible will be recorded

in a log with the reason of ineligibility and their enrollment status will be updated in OnCore. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants and to respond to queries from regulatory authorities. Minimal information includes demography, informed consent date, screen failure details, eligibility criteria, study discontinuation date, adverse events and any serious adverse event (SAE).
Eligible patients will be enrolled on study centrally at Winship Cancer Institute by the Study Coordinator.
When all required test results are available, complete the eligibility checklist and provide the checklist and the supporting documentation to the IRB approved investigator for review and sign-off. Once the investigator (sub-investigator, Co-Investigator) has signed the eligibility checklist, randomization and or enrollment may proceed. Oncore and ERMS must be updated to reflect eligibility and on treatment status.

Following enrollment, patients should begin protocol treatment within14 business days. Issues that would cause treatment delays should be discussed with the Principal Investigator.

The Eligibility checklist is to be printed from OnCore and verified by 2 people, of which one must be a clinical investigator or co-investigator. The completed and signed eligibility checklist along with all redacted supporting source documentation must be submitted to the Winship Multi-site Coordinator (MSC) or designee (fax 404-778-0417) within 14 days after pre-registration but no later than 2 business days before the scheduled treatment visit. Eligibility will be confirmed by the site investigator or co-investigator and the MSC or designee within 1 business day of receipt of all eligibility documentation and confirmation will be sent to the participating site along with cohort assignment, if subject meets criteria. The Participating Site will enter all data in OnCore following eligibility confirmation, including subject 'on treatment date'. If a consented subject does not meet eligibility criteria (screen failure), the MSC will update the enrollment status in OnCore. The Participating Site is responsible for entering data for all procedures subject completed prior to eligibility determination.

13.Withdrawal of Participants

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study intervention for **8 weeks**.
- Sponsor or Eisai terminate the study

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are enrolled but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are enrolled and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

14.Risks to Participants

The Adverse Event and Potential Risks list provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system.

Refer to the package inserts for the comprehensive list of adverse events.

Additional Risks:

- **Additional blood draws** - The physical risk of drawing blood is local pain and bruising at the site of venipuncture. Qualified phlebotomists or designee will draw blood samples. Care will be taken to obtain these specimens in a safe and hygienic manner. A small number of people experience lightheadedness or fainting. There is a slight risk of infection. To minimize these risks, attempts will be made to draw study blood samples at the same time as blood draws needed for routine clinical care are obtained. Repeated blood drawing may be associated with iron deficiency anemia.
- **Events of osteonecrosis of the jaw (ONJ)** have been observed with lenvatinib. Invasive dental procedures are an identified risk factor for the development of ONJ. An oral dental examination and appropriate preventive dentistry should be considered prior to initiation of lenvatinib. Patients should be advised regarding periodic dental examinations and oral hygiene practice during lenvatinib therapy. Avoid invasive dental procedures during lenvatinib treatment, if possible. Use caution in patients receiving agents associated with ONJ, such as bisphosphonates and denosumab.
- **Data security-** Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subjects' PHI. All records will be kept in a locked file cabinet or maintained in a locked room at the participating sites. Electronic files will be password protected behind an academic institutional firewall. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify subjects. Organizations that may inspect and/or copy research records maintained at the participating sites for quality assurance and data analysis include groups such as the National Cancer Institute (NCI) and Food and Drug Administration (FDA).

15.Potential Benefits to Participants

There is no guarantee of benefit to subjects who enroll in this protocol.

16.Data Management and Confidentiality

16.1 Statistical Consideration Data/specimens:

Study design

This is a Phase II, single arm, multi-institutional trial of lenvatinib in patients with recurrent HCC after liver transplant. The study will proceed using a Simon 2-stage Minimax design.

Sample size considerations

A Simon's 2-stage (Minimax) design will be adopted for a possible early termination for futility. Overall response rate (ORR) (complete response +partial response) will be the primary endpoint. The objective response rate with single agent Lenvatinib was 24.1% by mRECIST and 18.8% by RECIST version 1.1 in REFLECT trial[11]; however, the objective response rate in post-transplant recurrent HCC is not known. We hypothesize that there is >24% overall response rate and a rate <5% will be considered as futility. The Type I error rate is set at 5% and power of this study will be at least 80%. In the first stage, 11 patients will be accrued, and if there is no objective response among them, the study will be stopped for futility. Otherwise, additional 6 patients will be accrued for a total of 17 patients. The treatment will be determined to be ineffective if there are 2 or fewer responses in 17 patients at the end of the second stage enrollment. We require 3 or more patients out of the total of 17 subjects to achieve objective response for the investigational therapy to be deemed to have sufficiently improved clinical activity to justify further clinical development. We anticipate enrolling 1 patient per month. All patients will undergo baseline staging scan and restaging scan every 8 weeks. The treatment will continue until disease progression (using RECIST version 1.1 criteria), intolerable side effects or consent withdrawal. Given an anticipated attrition rate of approximately 10%, we expect to enroll an additional 2 patients, for a total of 19 patients.

Efficacy analysis

Primary endpoint

Overall response rate (ORR): Overall response rate will be assessed per RECIST version 1.1 (Tumor measurements will be performed every 8 weeks). ORR will be calculated as a proportion (complete responses + partial responses / total patients) along with a 95% confidence interval using the Clopper-Pearson method. Chi-square tests or Fisher's exact tests will be used to compare the efficacy in term of response rate across different groups stratified by biomarkers or other factors, respectively.

Secondary endpoints

Progression Free survival (PFS): Progression-free survival is defined as time from diagnosis to disease progression or death. Patients will be censored at time of last follow-up. PFS will be estimated using the Kaplan-Meier method and compared between different groups using the log-rank test, respectively. The PFS of each patient group at specific time points, such as 6 months, 1 year, 3 year, and 5 year, etc. will be also estimated alone with 95% CI using the Greenwood formula. Cox proportional hazards models will be further used in the multivariable analyses to assess the adjusted effect of response on the patients' PFS after adjusting for other factors. Interaction terms between these factors will also be tested for statistical significance. The proportional hazards assumption will be evaluated graphically and analytically with regression diagnostics. Violations of the proportional hazards assumptions will be addressed by use of time-dependent covariates or extended Cox regression models.

Overall survival (OS): Overall survival is defined as time from diagnosis to death. Patients will be censored at time of last follow-up. OS will be estimated using the Kaplan-Meier method and compared between different groups using the log-rank test, respectively. The OS of each patient group at specific time points, such as 6 months, 1 year, 3 year, and 5 year, etc. will be also estimated alone with 95% CI using the Greenwood formula. Cox proportional hazards models will be further used in the multivariable analyses to assess the adjusted effect of response on the patients' OS after adjusting for other factors. Interaction terms between these factors will also be tested for statistical significance. The proportional hazards assumption will be evaluated graphically and analytically with regression diagnostics. Violations of the proportional hazards assumptions will be addressed by use of time-dependent covariates or extended Cox regression models.

Duration of response (DR): Duration of response is defined as time from confirmation of a partial response (PR), complete response (CR) or stable disease (SD), until the disease has been shown to progress following treatment (progressive disease or PD). Summary statistics will be reported for DR including mean, median, standard deviation, and range.

Exploratory analysis

For the biomarker study, descriptive statistics will be first used to summarize biomarker endpoints, including peripheral blood samples. Biomarker data will also be displayed graphically, where appropriate. Depending on whether data is normally distributed, a t-test or Wilcoxon rank sum test will be used to compare each biomarker between any two groups stratified by response or other factors, respectively. General linear models (GLM) will be used to compare each biomarker between responders and non-responders with and without adjusting for other factors. Logistic regression models will be further employed to test the adjusted effect of biomarker on the response rate after adjusting for other factors.

Safety analysis

Safety will be assessed through adverse events, vital sign measurements, physical examinations, and clinical laboratory tests. Summary statistics will be presented for all safety analyses. Data for continuous parameters will be presented using descriptive statistics including sample size, mean, and median; standard deviation; and minimum and maximum. Categorical parameters be displayed using counts and percentages. Toxicities will be presented as worst toxicity per patient and will be reported as percent toxicity.

Analysis populations

The Efficacy and Safety Populations include all subjects enrolled in the study and who receive lenvatinib. The Efficacy Population will be used for analysis of the primary and secondary endpoints. All safety analyses will be performed on the Safety Population.

Interim analysis

Simon's 2-stage approach will be utilized, and an interim analysis for futility will occur. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. In the 1st stage, 11 patients will be accrued. If there are no responses, the study will be stopped. Otherwise, 6 additional patients will be accrued for a total of 17. This design yields a Type I error rate of 5% with 80% power when the true response rate is 24%.

16.2 Data/specimens:

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized

third party without prior written approval of the Principal Investigator. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.
Data and/or data forms will be submitted in the clinical management system - Online Collaborative Research Environment (ONCORE)- per Winship SOP 4.2 Data Completion Metrics.
All information in original records and certified copies of original records or clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial is considered source data. Source data are contained in source documents, which can be original records or certified copies of hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Case Report Forms (CRFs) - Source data may be collected in the source documents or entered directly onto the case report forms.

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be maintained for at least 2 years after the investigation is completed.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

Samples and data collected under this protocol may be used to study hepatocellular carcinoma Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

17.Provisions to Monitor the Data to Ensure the Safety of Participants

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The characteristics of an observed AE will determine whether the event requires expedited reporting **in addition** to routine reporting.

Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Classification of an Adverse Event

Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although

an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Adverse Event and Serious Adverse Event Reporting

Expectedness

Sponsor Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Adverse Event Reporting

From the time of treatment allocation through **30** days following cessation of treatment, all adverse events, that begin or worsen after informed consent, **must be recorded** by the investigator or designee at each examination on the Adverse Event case report forms/worksheets.
The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.
Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF/worksheet.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.
If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form (or EOT/SEC/Survival Information in NOVDD). The occurrence of adverse events should be sought by non-directive questioning of the patient (patient) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (patient) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) or Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)

6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 9.2 and which seriousness criteria have been met (include for NCDS trials).
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4. For phase I studies any AE that constitutes a DLT should be reported like a grade 3 and 4 adverse event. All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.
Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome. Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event.
Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.
Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF.
Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

Reporting to study supporter/IRB and or FDA.

Serious Adverse Event Reporting

For the time period beginning at treatment allocation through 30 days following cessation of treatment, or **30** days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the study drug, must be **submitted on an SAE form** and assessed by PI in order to determine reporting criteria to IRB, DSMC, FDA, supporter or IND Sponsor.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the IND sponsor and should be provided as soon as possible. The IND sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.
All subjects with serious adverse events must be followed up for outcome.
Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode.
An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the reporting period described above should only be reported to FDA/IRB if the investigator suspects a causal relationship to the study treatment.
All SAE's where the investigator suspects a causal relationship to the study treatment will be reported to the study supporter.

Information about all SAEs is collected and recorded on the **Serious Adverse Event Report Form**; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and submit the completed form.
Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

All SAEs for drug studies must be recorded on a MedWatch 3500 Form. SAE reports and any other relevant safety information are to be forwarded to the following

MedWatch 3500 Reporting Guidelines:
Note: MedWatch 3500 forms and other information related to MedWatch reporting are available at http://www.fda.gov/medwatch/index.html.
A copy of all 15 Day Reports and Annual Progress Reports is submitted to Eisai as required by FDA. Investigators will cross reference this submission according to local regulations to the Investigational Compound Number (IND, CSA, etc.) at the time of submission.

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Reporting Requirements for IND holder
For Investigator-sponsored IND studies, reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR, Part 312.32. Events meeting the following criteria need to be submitted to the FDA as Expedited IND Safety Reports.

7 Calendar-Day Telephone or Fax Report
The Sponsor-Investigator is required to notify the FDA of a fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of *investigational agents*. An unexpected adverse event is one that is not already described in the most recent Guidance for Investigator section of the Investigator's Brochure. Such reports are to be telephoned or faxed to the FDA, within 7 calendar days of the first learning of the event.

15 Calendar-Day Written Report
The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious unexpected adverse event that is considered reasonably or possibly related to the use of investigational agent.

Written IND Safety Reports with analysis of similar events are to be submitted to the FDA, within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 Form but alternative formats (e.g., summary letter) are acceptable.
FDA Fax number of IND Safety Reports: 1-(800)-FDA-1078.
The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

All Adverse Events will be reported to regulatory authorities, IRBs and investigators in accordance with all applicable global laws and regulations.

For participating subsites, adverse events collected at treatment visits are to be entered into OnCore no later than 14 calendar days after data collection.

Site investigators must report all SAEs and unanticipated problems to the sponsor-investigator within 24 hours of the participating site becoming aware of the event. The participating site will submit the MedWatch Form 3500A to the Winship regulatory staff and will also enter the data into OnCore within the specified timelines above. The Emory sponsor must review and sign off on the event and return to the Winship regulatory staff. Regulatory will review the assessment to determine IRB and/or FDA reporting requirements.

As applicable in multi-site studies, investigative sites at each institution should report serious adverse events to their respective IRB per local IRB policies and procedures. The subsite Principal Investigator will submit SAE reports from outside institutions to his/her institution's IRB per institutional guidelines.

Subsite SAE Reporting Requirements

Subsites are not permitted to report directly to the coordinating center IRB or FDA. All external site SAEs are to be reported to the coordinating center. The coordinating center multi-site coordinator will facilitate submission of external site SAEs to the coordinating center IRB and FDA.

All serious adverse events (SAEs) and other adverse events must be recorded on case report forms. In addition, all SAEs must be reported to the coordinating center principal investigator and coordinating center multi-site coordinator within 24 hours of knowledge of the event using the FDA MedWatch 3500A mandatory reporting form.

Copies of de-identified source documentation pertaining to the SAE must be submitted to the coordinating center. If a patient is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up form.

All SAEs must be submitted to the local IRB per local IRB and institutional policy.

Upon request of additional data or information that is deemed necessary must be reported to the coordinating center as soon as possible but no later than 5 calendar days.

Sponsor Investigator reporting to the Food and Drug administration (FDA)

The Sponsor Investigator, as holder of the IND (as applicable), will be responsible for all communication with the FDA. The Sponsor Investigator [or designee] will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.
Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but no later than 7 calendar days after initial receipt of the information.
All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information. Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800- FDA-0178) using MEDWATCH Form FDA 3500A (Mandatory Reporting Form for investigational agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

An annual safety report containing all SAEs, expected and unexpected, will be sent to the FDA and other applicable regulatory authorities.

Second and secondary malignancy

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

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

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.
A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy).

Definition of unanticipated problems (UP) and reporting requirements

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or an outcome that meets **all** the following criteria: Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. This study will use the OHRP definition of unanticipated problems. Incidents or events that meet the OHRP criteria for UPs require the creation and completion of a UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information: Protocol identifying information: protocol title and number, PI's name, and the IRB project number; A detailed description of the event, incident, experience, or outcome; An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP; A

description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP. The IND sponsor will make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

The Data and Safety Monitoring Committee (DSMC)

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

Multisite Monitoring Plan

At the time of study initiation at a non-Emory site, the Emory Sponsor, Winship regulatory specialist, and Winship research coordinators will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance. The participating site will have internal monitoring meetings. These meetings, which will include the participating site investigator, the clinical research coordinator and the regulatory affairs coordinator, will meet at least on a monthly basis to review and discuss study data to ensure subject safety. The research coordinators will maintain a spreadsheet which will be de-identified and will summarize all the patient data for subjects actively being treated on the trial as well as a roadmap detailing pending tests/treatments for each individual subject. The spreadsheet will be shared with the Emory PI via e-mail. Multi-Site Winship's MSC will perform an on-site or remote monitoring visit within the first three months of enrollment of the first subject. Quarterly monitoring visits will occur (once annually onsite and three times remotely) until subject follow-up is terminated. Monthly reviews of data in OnCore will be conducted

to ensure compliance or identify discrepancies. At least monthly teleconferences between Emory PI and participating site Teleconferences will be conducted at least once monthly between the PI at Emory and the research team at the participating site(s). The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. Scheduled teleconferences may stop after all patients have completed assigned protocol therapy. The PI at Emory will communicate with participating sites via monthly email. The minutes from the teleconference will be maintained in the regulatory binder for the study. In addition electronic copies will be sent via email to the principal investigators at each site.

18. Provisions to Protect the Privacy Interests of Participants

Participants will be assured of their voluntary participation in the study, their choice to answer or not answer any question, and the protocol for maintaining confidentiality.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived

19. Economic Burden to Participants

Lenvatinib will be free of charge to the participants. The study sponsor will pay for certain items and services the subject may receive in this study. Subjects will have to pay for the items or services for which the study sponsor does not pay. The sponsor will not pay for regular medical care. If subjects have insurance, Emory will submit claims to the insurance for items and services that the sponsor does not cover. Emory will send in only those claims for items and services that it reasonably believes the insurance will pay and that the sponsor has not paid. The actual amount that participants have to pay depends on whether or not they have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance companies will not pay for regular medical treatment or treatment for complications if in a study. If subject do not have insurance, Emory will review that particular case as part of its program for low-income patient care. The standard policies

of that program will apply. The program will figure out if subjects have to pay any costs for taking part in the study and what those costs will be

20. Consent Process

The initial informed consent discussion will occur in Winship Cancer Institute or the Emory Clinic.
At Winship Cancer Institute, the informed consent is an ongoing, interactive process rather than a one-time information session. The consent form document is designed to begin the informed consent process, which provides the patient with ongoing explanations that will help them make educational decisions about whether to begin or continue participating in the trial. The research team knows that a written document alone may not ensure that the patient fully understands what participation means. Therefore, the research team will discuss with the patient the trial's purpose, procedures, risks and potential benefits, and their rights as a participant. The team will continue to update the patient on any new information that may affect their situation.
Consent will be obtained prior to any research-driven procedures. The investigator will assess the patient's capacity during his/her encounters with him or her. The investigator will give the person providing consent adequate opportunity to read the consent document before it is signed and dated.
It will be explained to prospective participants that the study involves research, the purpose of the research, the expected duration of participation, as well as the approximate number of participants to be enrolled. The study procedures, and identification of research procedures v. non-research will also be thoroughly discussed. It will be explained to participants that participation is voluntary and that the subject may discontinue at any time.
Refusal to participate or withdraw will not involve a penalty or loss of benefits to which the participant is otherwise entitled. Refusal will in no way affect the participant's future are. The participant will also be told of the possible consequences of the decision to withdraw from the research, and procedures for orderly termination of participation.
Any significant new findings developed during the course of the research that may affect the participant's willingness to continue to participate will be provided. Also explained will be anticipated circumstances under which the subject's participation may be terminated by the investigator without the participant's consent.
Prospective participants will be provided with a description of any reasonably forseeable risks or discomforts as well as a description of any benefits to the participant or to others that might be reasons expected from the research. Alternative procedures or courses of treatment will also be thoroughly discussed.
Prospective participants will also be given detailed information describing the extent to which confidentiality of records identifying the participant will be maintained and what records may be examined by the research staff, IRBs, sponsor, their representatives, and possibly the FDA or OHRP.
Also communicated to the participant will be an explanation that emergency medical care will be arranged for a study-related illness or injury, and an explanation of whether funds are set aside to pay for this care and/or compensation, and if so by whom (e.g., sponsor, subject, insurer). The participant is told the source of the study's funding.
All participants will be told of any additional costs that may result from participation in the research.

Non-English-Speaking Participants

A certified translator/interpreter will be present during the consenting process and all questions and concerns will be answered by the treating physician.

A Short Form in that specific language will be used. A certified translator/interpreter will be present during the consenting process and this will be documented. We will use what's available on Emory IRB website. For the languages that are not available, we will have the short form translated to that language and submit the IRB for review and approval prior to use. Process to Document Consent in Writing: Winship SOP 2.1:"Obtaining Informed consent for Interventional clinical trial" will be followed.

Participants who are not yet adults (infants, children, teenagers): N/A

Cognitively Impaired Adults: N/A

Adults Unable to Consent: N/A

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception) N/A

21. Setting

The research will be conducted at Emory University, Mayo Clinic two sites (Mayo Clinic Arizona and Mayo Clinic Rochester) and the University of Alabama at Birmingham.

Potential participants will be identified in medical oncology clinics, multidisciplinary cancer clinic, surgical oncology clinics, multidisciplinary tumor board at Emory University, Mayo Clinic and the University of Alabama at Birmingham.

22. Resources Available

Emory University was founded in 1836 and is a national center for teaching, research, and service. Emory University has been named as one of the nation's top 25 universities for more than a decade by the U.S. News and World Report. Emory University research partners include the Georgia Institute of Technology, the University of Georgia, Morehouse School of Medicine, the US Centers for Disease Control and Prevention, Children's Healthcare of Atlanta, and the Georgia Clinical and Translational Science Alliance (GACTSA). Emory University researchers received $734 million from external funding agencies in fiscal year 2018, including approximately $441 million in funding from federal agencies, $359 million of this from the National Institutes of Health (NIH).

Winship Cancer Institute (Winship) is Georgia's first and only National Cancer Institute (NCI)-designated Comprehensive Cancer Center (P30CA138292) and is dedicated to the integration of innovative clinical and basic science research with outstanding patient care for the prevention, treatment and control of cancer. First designated in 2009, Winship's NCI designation was renewed in 2012 and 2016, achieving an "outstanding" rating. Winship earned the prestigious Comprehensive Cancer Center designation from the NCI in 2016, after demonstrating that its outstanding programs are reducing the cancer burden on the state of Georgia through research conducted in its laboratories, its clinical trial program, and its population-based science. The institutional support for Winship was rated as 'exceptional' by the review panel.

The **Winship Clinic Building C** houses the primary offices and clinical space for cancer services including the medical oncology, hematology, and surgical oncology clinics, the radiation oncology program, and the Winship Ambulatory Infusion Center. In summer 2017, Emory Healthcare completed the expansion of **Emory University Hospital Tower** on Clifton Road. This nine-floor facility adds 144 inpatient beds to the hospital, of which more than 80% are dedicated to cancer care. The hospital expansion also accommodates cancer patient-specific intensive care units, an expanded BMT Unit with peri-transplant clinics to facilitate continuity of care, and a 24-hour cancer urgent care center, which serves as both a triage facility and short stay treatment center for patients with cancer-related medical concerns.

The **Winship Phase I Unit**, on the fourth floor of the Emory University Hospital Tower, is the largest unit in Georgia dedicated to the earliest and most critical phase of new cancer therapy evaluation. There is space for 15 private treatment bays, four clinic rooms, its own lab for doing patient blood work, a dedicated secure medication room, computer workspace for research and other support staff, and a "fast track" bay with three chairs for rapid use in patients who, for example, might need only a research lab test done.

Mayo Clinic is the first and largest integrated, not-for-profit group practice in the world. Mayo Clinic has 65,214 total employees consisting of 4,878 physicians and scientists and 60,336 allied and administrative staff (not including students, fellows, and residents), with main campuses in Rochester, Minnesota; Jacksonville, Florida; and Scottsdale/Phoenix, Arizona; as well as more than 70 smaller hospitals and facilities (the Mayo Clinic Health System) across 6 states.

Mayo Clinic Cancer Center is the only NCI-designated Comprehensive Cancer Center with three geographic sites. It was one of the first cancer centers to receive the NCI designation in 1973. More than 122,000 cancer patients come to Mayo Clinic Cancer Center each year, where physicians, care providers and researchers – more than 1,000 of them – help patients find individualized solutions to address all aspects of their cancer journeys. Patients are cared for by a team of experts who address not only their cancer diagnoses, but their healthcare needs beyond cancer. Mayo Clinic Cancer Center patients have access to hundreds of clinical trials led by Mayo Clinic physicians and scientists. More trials are available through cooperative research agreements with the NCI and clinical trial study groups.

Mayo Clinic in Rochester, MN (MCR) is approx. 1,017,787 sq ft and Research laboratory space is approximately 390,250 sq. ft. Patient-oriented research is conducted in the Mayo and Gonda Buildings, and laboratory research is primarily conducted in the Guggenheim, Hilton, and Stabile Buildings. Dry laboratory research is conducted in the Charlton Building, the Plummer Building, and the Harwick Building. The Cancer Center controls more than 84,000 total sq ft on the Rochester campus in the Guggenheim, Charlton, Gonda, and Plummer Buildings, and the Mayo Support Center.

Mayo Clinic in Arizona opened in 1987 and is now located on 2 separate campuses. The research facilities and administration are located in Scottsdale, AZ, a suburb of Phoenix, a major metropolitan area of nearly 4 million people. The hospital facilities and the cancer center are located within the Phoenix city limits about 15 miles away. The hospital has a dedicated hematology/oncology inpatient unit. The cancer center building at the Phoenix campus houses medical oncology, radiation oncology, radiology, and nuclear medicine to ensure the multi-disciplinary care.

The O` Neal Comprehensive Cancer Center at University of Alabama at Birmingham offers a full array of treatment options from multidisciplinary clinics filled with experts from across cancer fields to the latest state-of-the-art technology. The center is home to an outstanding faculty of roughly 400 clinicians, scientists and clinician-scientists, many of whom are internationally and nationally recognized for their expertise in oncology. The O'Neal Cancer Center treats approximately 20,000 patients annually, with an estimated 5,000 new patients each year.

23. Multi-Site Research when Emory is the Lead Site

All sites will have the current protocol document and each IRB will review each site's consent form and all required approvals will be obtained at each site. Any protocol modifications will be communicated to all sites with the appropriate regulatory agencies notified for their respective reviews and approvals. All engaged participating sites will safeguard date, including secure transmission of data, as required by local information security policies. All local site investigators will conduct the study in accordance with applicable federal regulations and local laws. All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

Site initiation at subsites

At the time of study initiation at a subsite, the coordinating center multi-site coordinator (with additional staff as needed) will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance.

Subsite data collection

Subsite data must be submitted to the coordinating center multi-site coordinator as outlined in the protocol-specific monitoring plan. The protocol-specific monitoring plan will be provided by the coordinating center multi-site coordinator to external participating prior to site activation. Access to the coordinating center OnCore database will be provided to external participating sites for direct electronic data entry. All data submitted must be accompanied by supporting source documents, where applicable and as outlined in the protocol-specific monitoring plan. All data must be entered in the timeframe required at each site, but no later than 14 days following registration and each visit completion. All queries are to be resolved within 4 weeks of issue. The coordinating center multi-site coordinator will provide OnCore training and request access to the appropriate staff at the participating site.

Monthly investigator conference calls

The subsite research coordinators will maintain a spreadsheet which will be de-identified and will summarize patient data for subjects actively being treated on the trial well as a roadmap detailing pending tests/treatments for each individual subject. The spreadsheet will be shared with the coordinating center PI / IND sponsor (or designee) via e-mail. Teleconferences will be conducted at least once monthly between the PI (or designee) at Emory and the research team at the participating site(s).

The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. Scheduled teleconferences may stop after all patients have completed assigned protocol therapy. The coordinating center (or designee) will communicate with participating sites via monthly email.

The minutes from the teleconference will be maintained in the regulatory binder for the study. In addition electronic copies will be sent via email to the research teams at subsite.

Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial follows the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Subsite self-monitoring: The participating site will have internal monitoring meetings. These meetings which will include the participating site investigator (or designee), the clinical research coordinator and the regulatory affairs coordinator as applicable, will meet at least on a monthly basis to review and discuss study data to ensure subject safety. Chart reviews will be performed on selected cases by participating site staff to confirm that the data collection is accurate regarding study conduct, data collection, documentation and completion.

Central monitoring: Study-specific monitoring plans are specified per site, with the only difference between sites whether the site submits source data on paper or provides the coordinating center multi-site team remote access to that site's local electronic medical record. Centralized monitoring will occur minimally quarterly, no more frequently than monthly. Monitoring will be centralized, including data reporting and research sample acquisition. The coordinating center multi-site coordinator will perform on-site and/or remote monitoring visit within the first three months of enrollment of the first subject. Quarterly monitoring visits will occur (on site up to once per year and at least three times remotely) until subject follow-up is terminated. Monthly reviews of data will be conducted to ensure compliance or identify discrepancies; specifically, to assess compliance with the protocol, verify informed consent forms, verify compliance with SAE reporting procedures, monitor the tracking of study drug (pharmacy visit, storage and accounting of study drug), retrieve regulatory documentation, and perform quality control by comparing data from the CRF to the source documents of the center.

Auditing

For sites with an auditing mechanism in place that are able to share documentation of their auditing standards and processes followed, an agreement may be requested for the site to perform local auditing and provide formal audit reports to the coordinating center.

24. References

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair

APPENDIX B Drug Diary

Study ID:

[*Drug*] Pill Diary

Subject Initials:___ Subject ID: _____ Cycle: _____

Instructions:
Planned Daily Dose: __**mg**
REMINDERS:
1.
2.

Day	Date	Time	# of Tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Name of Medication	Why did you take the medication?	Date Medication Started	Date Medication Stopped

Record all medications taken during this cycle for example prescriptions and over the counter including vitamins.

Please sign at the completion of this cycle and **return with pill bottle** to the study team.

Patient's

Signature _____ Date_____

If you have any questions, please call: _____

APPENDIX C (RECIST Criteria v. 1.1)

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan,

D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

Appendix D CHILD-PUGH CLASSIFICATION

Child Pugh Score

Score	Points
Child-Pugh A	5-6
Child Pugh B	7-9
Child Pugh C	>9

Measure	1 point	2 points	3 points
Ascites	Absent	Slight	Moderate
Serum Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Serum bilirubin (mg/dL)	<2	2.0-3.0	>3
INR or Prothrombin time prolongation	<1.7 <4 sec	1.7-2.2 4-6 sec	>2.2 >6 sec
Encephalopathy	None	Grade I-II	Grade III-IV

Encephalopathy grade:

- Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
- Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
- Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
- Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
- Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity