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UMCC 2020.007

Phase 1/2 Trial to Evaluate Cabozantinib in Patients with Advanced Hepatocellular Carcinoma with Child Pugh Class B Cirrhosis after First-Line Therapy

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Study Drug: Cabozantinib (Cabometyx®)

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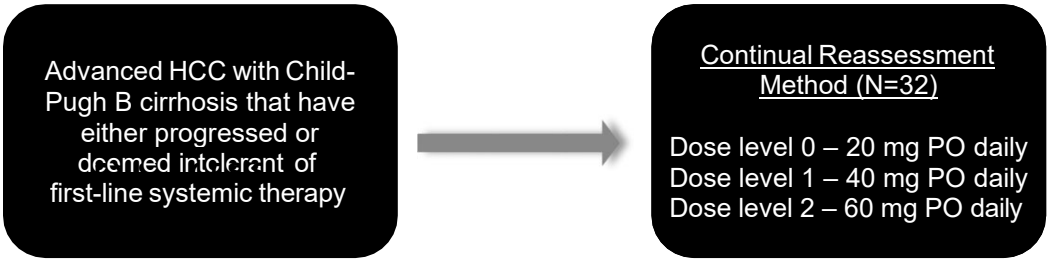
ABBREVIATIONS:

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTSU	Clinical Trials Support Unit
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
H&P	History & Physical Exam
HCC	Hepatocellular Carcinoma
HRPP	Human Research Protections Program
IND	Investigational New Drug
IRB	Institutional Review Board
IV (or iv)	Intravenously
MSPM	Multi-Site Project Manager
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PO	per os/by mouth/orally
PR	Partial Response
PRC	Protocol Review Committee
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SD	Stable Disease
TiTE-CRM	Time-To-Event modification of the Continual Reassessment Method
TTP	Time to Progression
UaP	Unanticipated Problem
WBC	White Blood Cells

STUDY SCHEMA



Title	Phase 1/2 Trial to Evaluate Cabozantinib in Patients with Advanced Hepatocellular Carcinoma with Child Pugh Class B Cirrhosis after First-Line Therapy
Phase	Phase I/II
Methodology	Single arm
Study Duration	3 years
Study Center(s)	Multi-Center: up to 4 sites total including lead site: University of Michigan
Objectives	**Primary Objectives** 1. Determine the maximum tolerated dose/recommended phase 2 dose (RP2D) for cabozantinib in patients with HCC with underlying Child-Pugh B cirrhosis **Secondary Objectives** 1. Evaluate the overall response rate, median TTP, PFS and OS of patients with advanced HCC. 2. Evaluate the safety and tolerability of cabozantinib in this patient population. 3. Characterize the pharmacokinetic (PK) profile of cabozantinib in this patient population **Exploratory Objectives** 1. To explore predictors of biomarker response and mechanisms of resistance based on the exploratory analysis of tumor tissue obtained through serial biopsies and blood, when available. a. Levels of PD-L1 (B7-H1), PD-L2, T cell subset, myeloid-derived cell subset infiltration by immunohistochemistry (IHC) at baseline, at 2 months and progression. b. Whole exome genomic and transcriptomic (RNAseq) analysis for MET, VEGF, AXL and immune signature at baseline, and progression, if tissue is available. c. Collection of blood in Streck tubes for plasma and PBMC collection for future cfDNA and immune cell subset analysis, respectively
Number of Subjects	32
Eligibility Criteria	See Section 3.1 for Eligibility Criteria.

Study Product(s), Dose, Route, Regimen	Cabozantinib 20-60 mg by mouth once daily
Duration of Administration	Patients may be treated on study for no longer than 2 years.
Statistical Methodology	This protocol will enroll patients with unresectable or metastatic, Child-Pugh B7 or B8 HCC to receive cabozantinib in a Phase 1/2 study to confirm the safety profile and the recommended Phase 2 dose (RP2D) in this patient population. The primary endpoint is the assessment of dose-limiting toxicity during the first 29-days of therapy. The secondary endpoints include ORR (PR+CR) per RECIST v1.1 criteria during active study treatment, safety, PFS and OS. PK assessment will also be completed for this cohort. The trial will be monitored using the Time-To-Event modification of the Continual Reassessment Method (TITE-CRM). This method assumes a model for the time to occurrence of toxic responses as a function of the dose. The time-to-event modification allows information from all patients enrolled and treated (even those with only partial observation) to contribute information for calculating the dose-toxicity relationship. This method is flexible with regard to the number of patients treated at each dose level, patients may be continuously recruited throughout the trial, without recruitment pauses, as long as patients are assigned a dose deemed safe at the time of enrollment.

1.0 BACKGROUND AND RATIONALE

1.1 Hepatocellular Carcinoma - Background

Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer related death worldwide (El-Serag and Rudolph 2007). In the U.S. it is increasing in frequency and highly morbid, accounting over 30,000 deaths per year. HCC typically develops in patients with cirrhosis, which partially accounts for the high mortality seen in this population, with 5-year survival estimates at 18-20%. Patients with early stage disease may be eligible for curative therapies, however the majority of patient present with late stage HCC. The first-line systemic therapies for HCC include multikinase inhibitors, sorafenib and lenvatinib. The phase 3 SHARP trial randomized patients with untreated HCC with underlying Child-Pugh A cirrhosis to either sorafenib or placebo and noted a median overall survival of 10.7 and 7.9 months (HR 0.69; P, <.001), respectively (Llovet, Ricci et al. 2008). More recently, a non-inferiority phase 3 trial randomized patients to either lenvatinib or sorafenib in the same patient population, and showed that overall survival was 13.6 versus 12.3 months (HR 0.92), respectively (Kudo, Finn et al. 2018).

After progression on sorafenib, five medications have received FDA approval in HCC. The phase 3 RESORCE trial evaluated regorafenib versus placebo in patients with HCC after sorafenib failure with Child-Pugh A cirrhosis and an ECOG performance status score of 0-1, and noted a median overall survival (OS) of 10.6 and 7.8 months (HR, 0.63; P, <.0001), respectively (Bruix, Qin et al. 2017). Nivolumab, an anti-PD1 immune checkpoint inhibitor, was evaluated in patients with unresectable HCC previously treated with sorafenib with Child-Pugh class A cirrhosis on the CheckMate040 trial, and was found to have an overall response rate (ORR) of 18.2%, and thus has gained FDA approval as a second-line therapy for unresectable HCC (El-Khoueiry, Sangro et al. 2017). Pembrolizumab, another anti-PD1 immune checkpoint inhibitor was also approved for second-line HCC therapy based on a 17% ORR in the phase-2 KEYNOTE 224 study (Zhu, Finn et al. 2018). Ramucirumab, a monoclonal antibody targeting VEGFR2, gained second line approval for patients with HCC and an alpha fetoprotein level greater than 400 based on the results of the Phase 3 REACH-2 study (Zhu, Kang et al. 2019). The phase 3 CELESTIAL trial evaluated cabozantinib versus placebo in patients with HCC after sorafenib failure with Child-Pugh A cirrhosis and an ECOG performance status score of 0-1, and noted a median overall survival (OS) of 10.2 and 8.0 months (HR, 0.76; P, .005), respectively (Abou-Alfa, Meyer et al. 2018).

1.2 Management of HCC Patients with Child-Pugh B Cirrhosis

There are no approved second-line systemic therapies in patients with more advanced cirrhosis (Child-Pugh classes B or C), which represents a significant proportion of patients who present with advanced HCC. In the GIDEON study, an international observational study of patients on sorafenib, over 20% of patients had Child-Pugh B cirrhosis at presentation (Lencioni, Kudo et al. 2014). There are minimal prospective data to evaluate the safety and efficacy of the currently approved second-line therapies for HCC in Child-Pugh B cirrhosis. An Italian prospective database on the use of sorafenib in patients with HCC with no prior therapy and underlying Child-Pugh A (n=234) and B (n=63) patients showed the Child-Pugh class B patients, regardless of disease spread, had a higher risk of death than those with Child-Pugh class A function (OS 3.8 versus 10.0 months (P, <.001), respectively). Moreover, Child-Pugh class B patients with a B8 + B9 score did worse in terms of OS compared with those with a B7 score. However, the median time to progression (TTP) in each respective arm was 4.2 and 3.8 months with no statistical significance. Additionally, the median daily dose between the 2 arms was also not statistically different and the study concluded that the drug is tolerable and patients with Child-Pugh class B may be safely treated with sorafenib (Pressiani, Boni et al. 2013).

However, there are no prospective trial data, and thus there is a significant unmet need for systemic therapeutic options in this patient population.

1.3 Rationale

Patients with unresectable HCC with underlying **Child-Pugh** class B cirrhosis have no options for systemic therapy based on current guidelines and available evidence. The aim of this study is to determine the safety and efficacy of cabozantinib in the management of HCC in this patient population.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 Determine the maximum tolerated dose/recommended phase 2 dose (RP2D) for cabozantinib in patients with HCC with underlying Child-Pugh B cirrhosis

2.2 Secondary Objectives

2.2.1 Evaluate the overall response rate, median TTP, PFS and OS of patients with advanced HCC.

2.2.2 Evaluate the safety and tolerability of cabozantinib in this patient population.

2.2.3 Characterize the pharmacokinetic (PK) profile of cabozantinib in this patient population

2.3 Exploratory Objectives

2.3.1 To explore predictors of biomarker response and mechanisms of resistance based on the exploratory analysis of tumor tissue obtained through serial biopsies and blood, when available.

a) Levels of PD-L1 (B7-H1), PD-L2, T cell subset, myeloid-derived cell subset infiltration by immunohistochemistry (IHC) at baseline, at 2 months and progression.
b) Whole exome genomic and transcriptomic (RNAseq) analysis for MET, VEGF, AXL and immune signature at baseline, and progression, if tissue is available.
c) Collection of blood in Streck tubes for plasma and PBMC collection for future cfDNA and immune cell subset analysis, respectively

2.4 Endpoints Assessment

2.4.1 Primary Endpoint Assessment: Determine the maximum tolerated dose/recommended phase 2 dose by assessment of dose-limiting toxicities (DLTs).

2.4.2 Secondary Endpoint Assessment: The progression-free survival (PFS) will be defined as time from date of treatment to date of radiological or clinical progression (leading to withdrawal from the study), or death from any cause, whichever comes first. The time to progression (TTP) will be defined as time from date of treatment to date of radiological or clinical progression (leading to withdrawal from the study). Follow-up time will be censored at the date of last disease evaluation. Overall survival (OS) will be defined from the date of treatment to either date of death or censoring. Adverse events and reportable serious events are defined by the study protocol (NCI Common Toxicity Criteria for Adverse Events (CTCAE) v5.0).

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the eligibility criteria to be enrolled to the study. Study treatment may not begin until a subject is enrolled.

3.1 Eligibility Criteria

3.1.1 Patients must have a radiologically consistent (early enhancement and delayed enhancement washout) or pathologically confirmed diagnosis of hepatocellular carcinoma that is not eligible for curative resection, transplantation, or ablative therapies.

3.1.2 Prior radiation, liver directed therapy (including bland, chemo- or radio-embolization, or ablation), or hepatic resection are permitted if $\geq$4 weeks from start of therapy. Extra-hepatic palliative radiation is permitted if completed $\geq$2 weeks prior to first dose of study therapy and the patient has recovered to $\leq$ grade 1 toxicity.

3.1.3 Patients must have radiographically measurable disease (RECIST1.1) in at least one site not previously treated or with progression after radiation or liver directed therapy (including bland, chemo- or radio-embolization, or ablation) either within the liver or in a metastatic site.

3.1.4 Patients must have either progressed or deemed intolerant of first-line systemic therapy. More than one line of systemic therapy is not permitted. The last dose should be at least 2 weeks from first dose of study therapy. Prior treatment may not contain cabozantinib.

3.1.5 Recovery to ≤ grade 1 from toxicities related to any prior treatments, unless the AEs were clinically non-significant and/or stable on supportive therapy

3.1.6 Must be ≥ 18 years of age.

3.1.7 Must have a Child-Pugh score of B7 or B8

3.1.8 Must have an ECOG performance status of 0-1.

3.1.9 Ability to understand and willingness to sign IRB-approved informed consent.

3.1.10 Willing to provide archived tissue, if available, from a previous diagnostic biopsy.

3.1.11 Must be able to tolerate CT and/or MRI with contrast.

3.1.12 Adequate organ function obtained ≤ 2 weeks prior to enrollment:

absolute neutrophil count	≥ 1200/mm^3
hemoglobin	≥ 8.5 g/dL
platelets	≥ 60,000/mm^3
serum creatinine	≤ 1.5 x ULN
creatinine clearance	≥ 40 mL/min
albumin	≥ 2.8 g/dL
AST/ALT	≤ 5.0 x ULN
total bilirubin	≤ 3.0 mg/dL
INR	≤ 2.3

3.1.13 Must not have uncontrolled ascites (requiring paracentesis within 3 months of screening) or hepatic encephalopathy requiring hospitalization (within 6 months of screening)

3.1.14 Must not have prior history of organ transplantation.

3.1.15 No known brain metastasis unless adequately treated with radiotherapy and/or surgery and stable for at least 4 weeks before registration. Eligible subjects must have been without corticosteroid treatment at the time of registration.

3.1.16 Must not have undergone a major surgery (e.g., GI surgery, removal or biopsy of brain metastasis) within 8 weeks before first dose of study treatment. Complete wound healing from major surgery must have occurred 1 month before first dose and from minor surgery (e.g., simple excision, tooth extraction) at least 10 days before first dose. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

3.1.17 Must not have an active second malignancy other than non-melanoma skin cancer or cervical carcinoma in situ. Patients with history of malignancy are eligible provided primary treatment of that cancer was completed > 1 year prior to enrollment and the patient is free of clinical or radiologic evidence of recurrent or progressive malignancy.

3.1.18 Must not have uncontrolled, significant intercurrent or recent illness including, but not limited to the following conditions:

a. Cardiovascular disorders:
    i. Congestive heart failure New York Heart Association Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias.
    ii. Uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment.
    iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) within 6 months before first dose.
    iv. Presence of known arterial aneurysm.
b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
    i. The subject has evidence of tumor invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (e.g., Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction.
    ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose. Note: Complete healing of an intra-abdominal abscess must be confirmed before first dose.
c. Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, or other history of significant bleeding (e.g., pulmonary hemorrhage) within 12 weeks before first dose.
d. Cavitating pulmonary lesion(s) or known endotracheal or endobronchial disease manifestation.
e. Lesions invading or encasing any major blood vessels except thromboses of portal/hepatic vasculature attributed to underlying liver disease and/or liver tumor.
f. Other clinically significant disorders that would preclude safe study participation.

i. Serious non-healing wound/ulcer/bone fracture.
ii. Uncompensated/symptomatic hypothyroidism.
iii. Known HIV

3.1.19 Must not have untreated or incompletely treated varices with bleeding or high risk for bleeding. Subjects treated with adequate endoscopic therapy (in accordance with institutional standards) without any episodes of recurrent overt GI bleeding requiring transfusion or hospitalization for at least 6 months prior to study entry are eligible.

3.1.20 Must not have a psychiatric illness, other significant medical illness, or social situation (such as involuntary incarceration) which, in the investigator's opinion, would limit compliance or ability to comply with study requirements.

3.1.21 Women must not be pregnant or breastfeeding since cabozantinib may harm the fetus or child. All females of childbearing potential (not surgically sterilized and between menarche and 1-year post menopause) must have a blood or urine test to rule out pregnancy within 2 weeks prior to registration.

3.1.22 Women of child-bearing potential (not surgically sterilized and between menarche and 1-year post menopause) and men must agree to use 2 methods of adequate contraception (hormonal plus barrier or 2 barrier forms) OR abstinence prior to study entry, for the duration of study participation, and for 4 months following completion of study therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.23 Prisoners or subjects who are involuntarily incarcerated, or compulsorily detained for treatment of either a psychiatric or physical (e.g. infectious disease) illness would be excluded.

3.1.24 Concomitant treatment with strong inducers or inhibitors of CYP3A4 is not allowed (see Appendix III). Patients must discontinue the drug(s) at least 14 days prior to first study dose on the study.

3.1.25 Concomitant anticoagulation with oral anticoagulants (e.g. warfarin, direct thrombin and factor Xa inhibitors), or platelet inhibitors (e.g. clopidogrel) is not allowed. The following anticoagulants are allowed:

a. Low dose aspirin
b. Prophylactic dose low molecular weight heparin
c. Therapeutic dose low molecular weight heparin is allowed in subjects without brain metastasis who have been on a stable dose for at least 6 weeks before the first dose of study therapy, and have had no clinically significant hemorrhagic complications from the anticoagulation regimen.

3.1.26 Must not have corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms per electrocardiogram (ECG) within 28 days before first dose of study treatment. Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility.

4.0 SUBJECT SCREENING AND ENROLLMENT PROCEDURES

Patient enrollment for this trial will be centrally managed by the Oncology Clinical Trials Support Unit (i.e. the Coordinating Center) of The University of Michigan Rogel Cancer Center as described below:

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on the Screening and Enrollment Log provided by the Coordinating Center.

It is the responsibility of the local site investigator to determine patient eligibility prior to submitting patient enrollment request to the Coordinating Center. After patient eligibility has been determined, a copy of the completed Eligibility Worksheet together with all the pertinent de-identified source documents will be submitted by the requesting site to the Coordinating Center, by email to CTSU-Oncology-Multisite@med.umich.edu.

A Multi-Site Coordinator of the Coordinating Center, who acts as the registrar, will review the submitted documents and process the enrollment. Sites should inform the Multi-Site Coordinator of a potential enrollment by 5 p.m. on the day prior to enrollment. Same day enrollments cannot be guaranteed.

The registrar will send an email to the requesting site registrar to confirm patient enrollment and randomization and to provide the study identification number and randomization number assigned to the patient. In addition, a copy of the completed Eligibility Worksheet signed and dated by the registrar will be sent back to the requesting site registrar.

Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log. These patients will not have study identification number assigned to them, and will not receive study treatment.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

Protocol treatment must start within 14 calendar days of enrollment otherwise the patient will be taken off study. Re-screening is allowed.

5.1.1 Dose Levels

Patients will receive therapy with cabozantinib starting at dose level 1. The safety profile of this agent has been previously evaluated in patients with HCC with underlying Child-Pugh A cirrhosis (6). Patients may continue treatment in absence of disease progression or unacceptable toxicity for no longer than 2 years.

Table 1. Dose Levels

Dose Level	Cabozantinib Dose (Q28 days)
0	20 mg PO Daily
1*	40 mg PO Daily
2	60 mg PO Daily

**starting dose level*

Cabozantinib must be taken on an empty stomach. Subjects must be instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib.

Subjects should be instructed to take their cabozantinib dose at approximately the same time every day. If a subject misses a dose, the dose may be taken later only if it is within 12 hours of when the missed dose should have been taken. The missed dose should not be made up if it is within 12 hours of the next scheduled dose.

Cabozantinib tablets should be swallowed whole with at least 8 ounces of water. The tablets should not be crushed. Grapefruit, grapefruit juice, seville oranges and their products should be avoided by subjects taking cabozantinib.

5.1.2 Dose Limiting Toxicities

A DLT will be any of the following occurring during the first 29 days of therapy, attributed (possibly, probably, or definitely) to the drug following day 1 treatment as assessed per the NCI CTCAE v5.0.

1. Grade 4 or greater hematological toxicity with the exception of uncomplicated grade 4 leukopenia/ neutropenia lasting <7 days)
2. Grade 3 or higher thrombocytopenia with bleeding
3. Grade 3 or greater febrile neutropenia.
4. Grade 3 or greater non-hematological toxicity, except nausea, vomiting, diarrhea (exception only when lasting <3 days, or without supportive care measures, such as anti-diarrheal medications), hyperbilirubinemia (secondary to biliary obstruction), alopecia, fatigue, and hypersensitivity reaction
5. Any death not clearly due to the underlying disease or extraneous causes.
6. Grade 3 or higher electrolyte abnormality that lasts >72 hours, or is clinically complicated, or does not resolve spontaneously or with conventional medical interventions.

Any dose modifications deemed necessary for patient safety during this period by the treating investigator would constitute a DLT for that patient – even if not meeting the explicit DLT definition as reported in Section 5.1.2. With completion of cycle 1, and following DLT determination (**yes vs. no**) on cycle 2 day 1, cycle 2 may begin.

Information on dose limiting toxicity events must be entered within one business day, recorded locally and entered into Case Report Forms (CRFs) on the web-based electronic data capture (EDC) system of the University of Michigan.

5.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Dose modifications are not allowed during cycle 1, days 0-29, during DLT determination. Any dose modifications deemed necessary for patient safety during this period by the treating investigator would constitute a DLT for that patient – even if not meeting the explicit DLT definition as reported in Section 5.1.2. Each patient will be assessed for the development of toxicity according to the Time and Events Table (Section 6.2). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Table 2. Cabozantinib Dose Modifications

Current Dose	Adjusted Dose
60 mg	40 mg
40 mg	20 mg

20 mg	Discontinue

5.2.1 Dose re-escalation to previous dose may be considered at the discretion of the investigator for grade 2-3 AEs which have resolved or recovered to grade 1 (or baseline) and deemed tolerable and easily managed by optimized supportive treatment. All dose reductions for grade 4 AEs will be permanent unless otherwise noted.

5.2.2 If more than one toxicity occurs requiring dose reduction, the dose administered should be based on the most severe toxicity.

5.2.3 Treatment delay of more than 42 days from last intended therapy will result in treatment discontinuation unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity per the discretion of the investigator.

5.2.4 If a patient experiences neutropenic fever at any point in the treatment cycle, chemotherapy will be delayed until ANC $\geq$ 1,000 and antibiotic treatment of the event is completed. When treatment resumes, consider one dose level reduction as per Table 2.

5.2.5 Dose will not be modified for cholangitis attributable to biliary obstruction/stent occlusion unless this occurs in the setting of $\geq$ grade 3 neutropenia.

5.2.6 Laboratory abnormalities that are not directly attributable to treatment (i.e., hyperglycemia) or not clinically relevant (i.e., lymphopenia) do not require modification of dosing.

Table 3. Dose Modifications for Hematologic Toxicity	
Hematologic Toxicity	**Dose Adjustment for Cabozantinib**
ANC ≥ 1000/mm^3 **AND** **Platelets ≥ 60,000/mm^3**	Treat as scheduled
ANC 500-999/mm^3 **OR** **Platelets 40-59,999/mm^3**	Hold cabozantinib up to a maximum of 28 days until ANC ≥ 1000/mm^3 AND platelets ≥ 60,000/mm^3 then consider resuming at next lower dose level as detailed in Table 2. If not resolved, then discontinue treatment.
ANC < 500/mm^3 **OR** **Platelets < 40,000/mm^3**	Hold cabozantinib up to a maximum of 28 days until ANC ≥ 1000/mm^3 AND platelets ≥ 60,000/mm^3 then resume at next lower dose level as detailed in Table 2. If not resolved, then discontinue treatment.
Note: Laboratory abnormalities that are not directly attributable to treatment (i.e., basophilia), anemia, or not clinically relevant (i.e., lymphopenia) do not require dose modification. All dose adjustments for toxicity will be described in the clinical record.	

Table 4. Dose Modifications for Non-Hematologic Toxicity		
Non-Hematologic Toxicity	**Criteria**	**Dose Adjustment for Cabozantinib**
Alopecia	Any Grade	No modification to doses
Venous thromboembolism	Any Grade	Hold cabozantinib until anticoagulation has been established. No modification to doses. Low molecular weight heparins are the preferred management for thrombotic events; oral anticoagulants (e.g., warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines) are not allowed.
Arterial thromboembolism	Grade ≥3	Discontinue cabozantinib
Visceral perforation or fistula formation	Any Grade	Discontinue cabozantinib
Reversible posterior leukoencephalopathy syndrome	Any Grade	Discontinue cabozantinib

Wound dehiscence	Any Grade	Hold cabozantinib until complete healing has taken place
Nausea and vomiting	Grade >3 (ongoing after maximal anti-emetic therapy)	Consider decrease or discontinuation of cabozantinib
Hyperbilirubinemia	Grade ≥3	Hold cabozantinib up to a maximum of 42 days until toxicity resolves to Grade ≤ 2, then consider resuming at same dose as before. If not resolved, then discontinue all treatment. Dose will not be modified for cholangitis attributable to biliary obstruction/stent occlusion unless this occurs in the setting of >grade 3 neutropenia
Diarrhea	Tolerable Grade 1-2	• Continue with study treatment and consider dose reduction • Initiate treatment with an antidiarrheal agent (e.g., loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]) • Dietary modifications (e.g., small lactose-free meals, bananas and rice) • Intake of isotonic fluids (1-1.5 L/day) • Re-assess after 24 hours: o Diarrhea resolving to baseline bowel habits: gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 h diarrhea-free interval o Diarrhea not resolving: Continue/resume antidiarrheal treatment
	Intolerable Grade 2, Grade 2 > 48 h, or ≥ Grade 3	• Interrupt study treatment • Ask subject to attend clinic • Rule out infection (e.g., stool sample for culture) o Administer antibiotics as needed (e.g., if fever or Grade 3-4 neutropenia persists > 24 h) • Administer fluids (1-1.5 L/day orally or IV, as appropriate) for hydration or to correct electrolyte abnormalities • For Grade 3-4 or complicated lower grade diarrhea consider hospitalization and IV hydration • Re-assess after 24 h o Diarrhea resolving to baseline bowel habits or Grade ≤ 1: consider restarting study treatment at reduced dose Diarrhea not resolving: Start and or continue antidiarrheal treatment (e.g., loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]). Consider starting second line antidiarrheal or referral to gastroenterologist

Hemorrhage	Serious and life-threatening bleeding events or recent hemoptysis (≥ 2.5 mL of red blood)	Cabozantinib should be discontinued.
Hypertension	> 150 mm Hg (systolic) and < 160 mm Hg OR > 100 mm Hg (diastolic) and < 110 mm Hg	• Optimize antihypertensive medications by adding new or additional antihypertensive medications and/or increase dose of existing medications. • Reduce cabozantinib treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP <150 mm Hg systolic or <100 mm Hg diastolic • If subject is symptomatic interrupt cabozantinib treatment
	≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce cabozantinib by one dose level or interrupt cabozantinib treatment per investigator discretion • Add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, cabozantinib treatment should be dose reduced further or interrupted • Cabozantinib treatment should be dose interrupted if upper limits of systolic BP (≥ 160 mm Hg) are sustained and not adequately manageable or if systolic BP is > 180 mm Hg or diastolic BP > 110 mm Hg, or if subject is symptomatic • Re-start cabozantinib treatment at the most tolerable dose and re-escalate only if BP falls to and is sustained at < 150 mm Hg systolic and < 100 mm Hg diastolic
	Hypertensive emergency	• Discontinue cabozantinib treatment
Hand-Foot Syndrome	Grade 1	• Cabozantinib treatment may be continued at the current dose if PPES is clinically insignificant and tolerable. Otherwise, cabozantinib should be reduced to the next lower dose level. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPES worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.

	Grade 2	• Cabozantinib treatment may be continued if PPES is tolerated. Cabozantinib should be dose reduced or interrupted if PPES is intolerable. Continue urea 20% cream twice daily AND high potency steroid cream (e.g., clobetasol 0.05%) once daily and add analgesics (e.g., NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPES worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
	Grade 3	• Interrupt cabozantinib treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with high potency steroid cream (e.g., clobetasol 0.05%) twice daily AND analgesics. Resume study drug at a reduced dose if PPES recovers to Grade ≤ 1. Discontinue subject from study treatment if PPES does not improve within 6 weeks.
Proteinuria	≤ 1 mg/mg (≤ 113.1 mg/mmol)	• No change in cabozantinib treatment or monitoring
	> 1 and < 3.5 mg/mg (> 113.1 and < 395.9 mg/mmol)	• Consider confirming with a 24-h protein assessment within 7 days • No change in cabozantinib treatment required if UPCR ≤ 2 mg/mg or urine protein ≤ 2 g/24 h on 24-h urine collection. • Dose reduce or interrupt cabozantinib treatment if UPCR > 2 mg/mg on repeat UPCR testing or urine protein > 2 g/24 h on 24-h urine collection. Continue cabozantinib on a reduced dose if UPCR decreases to < 2 mg/mg. Consider interrupting cabozantinib treatment if UPCR remains > 2 mg/mg despite a dose reduction until UPCR decreases to < 2 mg/mg. Restart cabozantinib treatment at a reduced dose after a dose interruption. • Repeat UPCR within 7 days and once per week. If UPCR < 1 mg/mg on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and can be done within 1 week of first reading.) If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
	Nephrotic syndrome	• Discontinue cabozantinib treatment
Osteonecrosis (including jaw)	Grade 1-4	• Discontinue cabozantinib treatment

Other toxicity possibly attributable to study treatment	Intolerable Grade 2 that cannot be adequately managed	• Hold treatment or dose reduction at discretion of treating investigator. • Note: It is recommended that dose holds be as brief as possible.
	Grade 3	• Hold treatment and monitor toxicity every 1-2 weeks. If toxicity resolves to ≤ Grade 1 (or baseline) within 6 weeks, treatment may be resumed with one dose level reduction. • Note: It is recommended that dose holds be as brief as possible.
	Grade 4	• Discontinue cabozantinib unless the following criteria are met: o Subject is deriving clear clinical benefit as determined by the investigator o Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care
Note: Laboratory abnormalities that are not directly attributable to treatment (i.e., hyperglycemia), or can be managed easily (e.g. hypokalemia), or are not clinically relevant do not require dose modification. All dose adjustments for toxicity will be described in the clinical record.		

5.3 Concomitant Medications/Treatments

The following concomitant medications or treatments are not permitted while the patient is currently receiving therapy on the protocol:

- Other investigational agents or anticancer treatment
- Concurrent radiation or other locoregional therapy
- Strong CYP3A4 inhibitors and inducers (see Appendix III)
- Oral anticoagulants (e.g., warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents such as clopidogrel, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines).
- Erythropoietic stimulating agents (e.g., epoetin alfa and darbepoetin alfa)

The following concomitant medications or treatments are to be used with caution while the patient is currently receiving therapy on the protocol:

- Drugs that prolong the QTc interval should be avoided if possible, as cabozantinib can prolong the QTc interval
- Drugs known to be P-glycoprotein substrates (e.g. fexofenadine, aliskiren, ambrisentan, digoxin, colchicine, maraviroc, posaconazole, tolvaptan, etc.) should be used with caution as cabozantinib can cause increased P-glycoprotein substrate plasma concentrations.
- MRP2 inhibitors such as cyclosporine, delavirine, efavirenz, and emtricitabine should be used with caution during treatment with cabozantinib as coadministration can cause increased cabozantinib plasma concentrations.
- Highly protein-bound medications (e.g. diazepam, furosemide, dicloxacillin, propranolol, etc.) should be used with caution during treatment with cabozantinib.
- Grapefruit, star fruit, and seville oranges may also increase plasma concentrations of cabozantinib and should be avoided.

5.4 Other Modalities or Procedures

None

5.5 Duration of Therapy

Treatment may continue for a total of 2 years or until one of the following criteria apply:

- Disease progression as defined in Section 7.0
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (e.g., male condom, female condom) during the course of the study and for 4 months after discontinuation of study treatment
- Patient who becomes pregnant or is breastfeeding
- Patient who cannot tolerate the minimum protocol-specified dose of study treatment
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol
- Significant noncompliance with the protocol schedule in the opinion of the investigator
- Patient voluntarily withdraws from treatment **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

5.6 Off Treatment Criteria

Patients will be removed from protocol therapy when any of the criteria listed in Section 5.5 apply. Document in the source the reason for ending protocol therapy and the date the patient was removed from treatment. All patients who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 5.7. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

5.7 Duration of Follow-Up

After treatment discontinuation, follow-up for survival and initiation of any other anti-cancer therapies will be documented every 3 months (+/- 1 week) via telephone or office visit documentation for up to 2 years from treatment discontinuation or until death, whichever comes first, or 3 years after first date of treatment initiation for those that remain on treatment. Patients removed from treatment for unacceptable adverse events will also be followed more closely until resolution or stabilization of the adverse event.

5.8 Off Study Criteria

Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation from study will be documented and may include:

5.8.1 Patient withdraws consent (termination of treatment and follow-up);

5.8.2 Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;

5.8.3 Termination of the study by the Sponsor, the University of Michigan, or the FDA;

5.8.4 Patient completes protocol treatment and follow-up criteria;

5.9 Patient Replacement

All patients who receive at least one dose of study therapy will be considered evaluable for primary endpoint and safety/toxicity.

Patients enrolled in the study will be considered non-evaluable for efficacy under the following case scenarios and replaced by additional patients:

1. Patients who received no investigational therapy.

2. Patients meeting off study criteria 5.8.1 and 5.8.2. As this trial assigns the dose level based upon real-time assessment of the experience of those treated on trial, any partial data from a patient stopping trial therapy early while still within the observation period for dose-limiting toxicity due to criteria 5.8.1 and 5.8.2, will continue to have their partial data used for dose assignments for future patients. However, this type of patient, stopping treatment due to 5.8.1 and 5.8.2 would be replaced to reach the trial's total sample size.

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical

indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

6.2 Time and Events Table/Schedule of Events/Study Calendar

Table 5. Study Calendar							
Procedures	**Screening[1]**	**Cycle 1**		**Cycle X**		**EOT Visit[8]**	**Follow-Up Q3 months +/- 1 week[9]**
		Day 1	**Day 15**	**Day 1**	**Day 15**		
Informed Consent	X						
History, Physical Examination	X	X		X		X	
Weight, BSA	X	X		X		X	
Vital Signs	X	X	X	X		X	
Performance Status	X	X		X		X	
Toxicity Evaluations		X	X	X			
Scans with Tumor Measurements	X			X[5]			
CBC with differential	X	X	X	X			
CMP[2]	X	X	X	X			
AFP		X		X[10]		X	
PT/INR, PTT	X						
Pregnancy Test[3]	X						
UPCR[11]		X		X			
TSH, Free T4 and T3		X		X			
Concomitant Medication Review	X	X		X			
12 lead ECG	X						
PK Blood[12]			X	X[12]	X[12]		
Research Blood[4]		X		X		X	
Tissue[6]	X						X
Study Drug Administration[7]		X	X	X			
Survival Follow-up							X

1. All screening procedures to be completed within 2 weeks of enrollment, except imaging which should be ≤ 4 weeks. Protocol treatment is to begin ≤14 days of enrollment.

2. Comprehensive metabolic panel includes BUN/creatinine, sodium, potassium, chloride, glucose, calcium, alkaline phosphatase, AST, ALT, total bilirubin and total protein.
3. Required for females of childbearing potential. Serum or urine pregnancy test per site investigator discretion.
4. Cycle 1 Day 1 specimens will be collected prior to administration of initial dose, and Cycle X Day 1 specimens will be collected on Cycle 4 Day 1. Refer to the lab manual for sample collection and processing details.
5. MRI or CT (abdomen/pelvis) with contrast along with CT chest with/without contrast will be assessed every 8 ± 1 weeks starting from C1D1. Imaging assessment of scans at the site should be completed by either a radiologist or an imaging core, and not by the oncologist nor via abstraction of data from the subjective/clinical radiology report.
6. Pre-treatment, diagnostic pathology specimens obtained in the course of standard biopsy or surgery, if available. Procurement of tissue is mandatory for enrollment, if available. If tissue from initial biopsy is not available, a repeat biopsy is NOT required and patient will be eligible for enrollment. Post-treatment tissue collection, if available. Refer to the lab manual for sample collection and processing details.
7. See Section 5.1 for details. Study drug administration with associated labs will have a window of ± 3 days.
8. End of treatment (EOT) visit should be completed within 30 days of last treatment.
9. Patients will be followed every 3 months via telephone or office visit documentation for up to 2 years from treatment discontinuation or until death, whichever comes first, or 3 years after first date of treatment initiation for those that remain on treatment.
10. Check AFP every 8 +/- 1 weeks. May be delayed if drug is not administered within the window.
11. Urine protein/creatinine ratio
12. Pharmacokinetic blood draws (pre-dose) prior to Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15 and Cycle 3 Day 1. See lab manual for details.

7.0 MEASUREMENT OF EFFECT

7.1 Antitumor Effect- Solid Tumors

Objective response assessment will be determined by review of CT or MR scans of the chest, abdomen and pelvis using RECIST v1.1 every 8 weeks +/- 1 week while patients are on treatment (Eisenhauer, Therasse et al. 2009) .

7.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with study drug.

Evaluable for primary endpoint, DLT/MTD assessment. All patients that receive at least one dose of study therapy will be considered evaluable. Patients enrolled to therapy but that never receive study therapy will be replaced.

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

7.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) for studies with a slice thickness of ≤5mm or twice the slice thickness or MRI
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung)

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

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

Note: Tumor lesions that are situated in a previously irradiated area will only be considered measurable, if they have had subsequent progression by at least 5 mm.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm using CT scan), are considered non-measurable disease. Bone lesions without measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total should be identified as target lesions and recorded and

measured at baseline. Target lesions should be selected on the basis of their size (non-nodal lesions with the longest diameter), be representative of all involved organ(s), but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. Pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the nodal measurement. All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as 'present', 'absent', or in **rare** cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

7.1.3 Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start date and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and >10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

CT, MRI: MR is the best currently available and reproducible method to measure lesions selected for response assessment in HCC. If CT is completed, the guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

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

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response.

7.1.4 Response Criteria

7.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions (with a minimum absolute increase of 5 mm), taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

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

7.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes should be non-pathological in size (<10 mm short axis)

Non-CR/Non-PD: Persistence of one or more non-target lesion(s)

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

Although a clear progression on non-target lesions in absence of stable target lesions is exceptional, *the opinion of the treating physician should prevail in such circumstances*.

7.1.4.3 Evaluation of Best Overall Response

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

Table 6. Response Evaluation as per RECISTv1.1

Target Lesions	Non-Target Lesions	New Lesions	Overall Response per RECISTv1.1	Confirmed Response for this Category Requires:
CR	CR	No	CR	>4 wks. confirmation
CR	CR Non-CR/PD	No	PR	≥4 wks. confirmation
PR	CR Non-CR/PD	No		
SD	CR Non-CR/PD	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Any	PD	
Any	PD*	Any		
Any	Any	Yes		

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

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

NA=not applicable

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

7.1.5 Duration of Response

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

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

7.2 Safety/Tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 5.0 for reporting of adverse events (http://ctep.cancer.gov/reporting/ctc.html).

8.0 ADVERSE AND OTHER REPORTABLE EVENTS

8.1 Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial study treatment administration through 100 days after the last dose of study treatment. Any serious adverse event that occurs more than 100 days after the last study treatment and is considered related to the study treatment or intervention must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study treatment administration is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 8.3, occurring from the initial study treatment administration through 100 days following the last dose of the study treatment must be recorded as an adverse event in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study treatment or intervention. However, with regards to laboratory and vital sign abnormalities, only those which require protocol treatment to be modified or treatment to be rendered should be reported as AEs

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins study treatment is also considered an adverse event. However, anticipated fluctuations of pre-existing conditions, including the disease under study, that don't represent a clinically significant exacerbation or worsening, need not be reported as AEs.

8.2 Definitions

8.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an

abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

- Diagnostic and therapeutic non-invasive and invasive (i.e., surgical) procedures will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an adverse event unless it is a pre-existing (prior to protocol treatment) condition.

8.2.2 Serious Adverse Event

An adverse event is considered "serious" if, in the view of either the investigator or sponsor-investigator, it results in any of the following outcomes:

- Death
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- A life-threatening adverse event
  An adverse even is considered 'life-threatening' if, in the view of either the investigator [or sponsor], its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization for $\geq$ 24 hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical event: Any event 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 patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of "Serious Adverse Event". Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

8.2.3 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
   AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.2.4 Expected Adverse Events

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure.
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1.9 for the list of expected adverse events related to the drug under study.

8.2.5 Unexpected Adverse Event

An adverse event (AE) is considered "unexpected" if it is not described in the Package Insert, Investigator's Brochure, in published medical literature, in the protocol, or in the informed consent document.

8.3 Adverse Event Characteristics

8.3.1 CTCAE Term

(AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be down loaded from the CTEP web site. (http://ctep.cancer.gov)

8.3.2 Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.

RELATED

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

UNRELATED

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

8.4 Serious Adverse Event Reporting Guidelines

8.4.1 Reporting procedures for multi-site trials

All serious adverse events (SAEs) and unanticipated problems (UPs), regardless of causality to study drug, will be reported to the Principal Investigator and also to the Coordinating Center. All SAEs and UPs must be reported to the Coordinating Center within 1 business day of first awareness of the event. Events should be

reported using the Coordinating Center's SAE form as available in the study database. A copy of the SAE form as available in the study database should be sent to the Coordinating Center via fax at 734-232-0744 or via email to CTSU-Oncology-Multisite@med.umich.edu within 1 business day of the site's knowledge of the event.

Follow-up information must also be reported within 1 business day of receipt of the information by the investigator.

All SAEs and UPs will be reported to the IRB per current institutional standards.

The Coordinating Center will disseminate information regarding SAEs and UPs to the participating sites within 5 business days of review of the information by the Coordinating Center's Principal Investigator (or designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study drug. The Coordinating Center will be responsible for reporting of events to the FDA and supporters, as appropriate (outlined below).

8.4.2 Reporting procedures to Exelixis

All Serious Adverse Events (SAEs) occurring from the initial study treatment administration through 30 days following the last dose of the study treatment will be reported by the Coordinating Center to Exelixis. Any SAEs occurring after 30 days following the last dose of the study treatment that are believed to be related to study drug will also be reported to Exelixis.

The Coordinating Center will send the initial completed SAE Form within 1 business day of receipt via email to drugsafety@exelixis.com or fax 650-837-7392.

If only limited information is initially available or an ongoing SAE changes in its intensity or relationship to the study drug, or if new information becomes available, a follow-up report will be generated and sent to Exelixis within 1 business day of receipt.

Pregnancy (in subject or partner) or lactation exposure, although not an SAE, should be reported to Exelixis. Forms will be provided to the study sites upon request. The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to Exelixis. Any birth defect or congenital anomaly must be reported as an SAE, and any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.

8.5 Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

8.6 Reporting of Pregnancy

Pregnancies that occur during study participation or within 6 months of last study dose should be reported to the Coordinating Center via e-mail at CTSU-Oncology-Multisite@med.umich.edu immediately upon site's knowledge of the event.

8.7 Reporting of Unanticipated Problems

There are types of incidents, experiences and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered

adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the IRB within 14 calendar days of the study team becoming aware of the problem.

8.8 Safety Report Reconciliation

The Sponsor will reconcile the clinical database SAE reports transmitted to Exelixis. Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. Exelixis will email, upon request from the Investigator, the reconciliation report. Requests for reconciliation should be sent via email. The data elements listed on the reconciliation report will be used for identification purposes.

8.9 Stopping Rules

The DSMC comprised of the principal investigators, co-investigators at University of Michigan, study statistician, and multi-site coordinator will be responsible for the continuous monitoring of the study for treatment tolerability and efficacy. During the monthly meetings current study data will be reviewed and the decision to continue, hold, or stop accrual to this study will be formally considered.

9.0 DRUG INFORMATION

9.1 Cabozantinib

9.1.1 Other Names

Cabometyx®

9.1.2 Classification

Tyrosine kinase inhibitor/Antineoplastic agent

9.1.3 Mechanism of Action

Inhibition of the tyrosine kinase activity of MET, VEGFR-1, -2 and -3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2.

9.1.4 Pharmacokinetics

1. Distribution: The oral volume of distribution (Vz/F) of cabozantinib is approximately 319 L. Cabozantinib is highly protein bound in human plasma (≥ 99.7%).

2. Elimination: The predicted terminal half-life is approximately 99 hours and the clearance (CL/F) at steady state is estimated to be 2.2 L/hr.

9.1.5 Storage, Preparation and Stability

Cabozantinib can be stored at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F).

9.1.6 Dose and Administration

1. Dosage: See Section 5.1
2. Administration: Cabozantinib must be taken on an empty stomach. Subjects must be instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib. Subjects should be instructed to take their cabozantinib dose at approximately the same time every day. If a subject misses a dose, the dose may be taken later only if it is within 12 hours of when the missed dose should have been taken. The missed dose should not be made up if it is within 12 hours of the next scheduled dose.

   Cabozantinib tablets should be swallowed whole with at least 8 ounces of water. The tablets should not be crushed. Grapefruit, grapefruit juice, Seville oranges and their products should be avoided by subjects taking cabozantinib.

9.1.7 Availability

Cabozantinib tablets are supplied as film coated tablets containing cabozantinib malate equivalent to 20 mg and 60 mg of cabozantinib and contain microcrystalline cellulose, lactose anhydrous, hydoxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry® yellow.

60 mg tablets are yellow film-coated, *oval* shaped with no score, debossed with “XL” on one side and “60” on the other side of the tablet; available in bottles of 30 tablets: NDC 42388-023-26

20 mg tablets are yellow film-coated, *round* shaped with no score, debossed with “XL” on one side and “20” on the other side of the tablet; available in bottles of 30 tablets: NDC 42388-024-26

Doses of 40 mg will comprise of two 20-mg tablets.

9.1.8 Handling and Disposal

Cabozantinib disposal should occur in accordance with recommendation from the Food and Drug Administration. (https://www.fda.gov/drugs/safe-disposal-medicines/disposal-unused-medicines-what-you-should-know)

9.1.9 Adverse Effects

1. Adverse Effects: Adverse reactions occurring in ≥ 20% of cabozantinib-treated patients in the CELESTIAL clinical trial in patients with HCC, in order of decreasing frequency were: diarrhea, decreased appetite, palmar-plantar erythrodysesthesia (PPES), fatigue, nausea, hypertension, and vomiting (Abou-Alfa, Meyer et al. 2018). Grade 3-4 adverse reactions which occurred in ≥ 5% of patients were PPES, hypertension, fatigue, diarrhea, asthenia, and decreased appetite. There were 6 adverse reactions leading to death in patients receiving cabozantinib (hepatic failure, hepatorenal syndrome, esophagobronchial fistula, portal vein thrombosis, pulmonary embolism,

upper gastrointestinal hemorrhage). Other described AEs include GI fistulas and perforation (1%), thrombotic events (7%), jaw osteonecrosis (<1%), wound complications in the perioperative period, and Reversible Posterior Leukoencephalopathy Syndrome.

For a full description of the safety profile of cabozantinib across multiple cancers, refer to the Cabozantinib Investigator's Brochure.

Adverse events may occur within the first few weeks in the course of treatment with cabozantinib, as cabozantinib is expected to reach steady state exposure at approximately 2 weeks following first dose. Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting.

2. Pregnancy and Lactation: Category D. Based on animal data cabozantinib can cause fetal harm when administered to a pregnant woman.

3. Drug Interactions:
Strong CYP3A4 Inhibitors: Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inhibitor increased the exposure of cabozantinib, which may increase the risk of exposure-related adverse reactions. Avoid coadministration of cabozantinib with strong CYP3A4 inhibitors. Reduce the dosage of cabozantinib if coadministration with strong CYP3A inhibitors. Reduce the dosage of CABOMETYX if coadministration with strong CYP3A4 inhibitors cannot be avoided. Avoidance of grapefruit or grapefruit juice is recommended due to the potential for increased exposure of cabozantinib.

Strong CYP3A4 Inducers: Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inducer decreased the exposure of cabozantinib, which may reduce efficacy. Avoid coadministration of cabozantinib with strong CYP3A4 inducers. Increase the dosage of cabozantinib if coadministration with strong CYP3A4 inducers cannot be avoided. Avoidance of St. John's Wort is recommended which may lead to decreased exposure of cabozantinib.

10.0 CORRELATIVES/TRANSLATIONAL STUDIES

We will aim to study the HCC tumor microenvironment through the use of pre-treatment tissue collection (mandatory, if available, at all sites) as well as post-treatment tissue collection (optional for patients enrolled at all sites). Identification of important biologic subsets of HCC patients that may have clinical efficacy from cabozantinib will be the overarching goal of this translational science. Tissue (previously collected via core biopsy, surgical excision) may be examined by whole exome analysis, RNA seq and histologically by immunohistochemistry (IHC). Biologic markers and RNA expression will be examined in the context of patient efficacy.

10.1 Pharmacokinetic Analysis

The pharmacokinetic blood draws occur prior (pre-dose) to Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15 and Cycle 3 Day 1. See lab manual for details.

10.2 Tissue Collection

Tissue will be collected at the time points specified in section 6.2 Study Calendar. Please refer to the lab manual for sample collection and processing details.

10.3 Blood Collection

Blood samples will be collected at the time points specified in section 6.2 Study Calendar. Please refer to the lab manual for sample collection and processing details.

10.4 Centralized Imaging

All CT scans will be coded using trial patient and site IDs and shipped or electronically uploaded for banking and exploratory endpoint assessment. Please see the lab manual for details regarding shipping address and/or information for electronic upload.

10.5 Specimen Banking

Patient samples collected for this study will be retained at University of Michigan. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

Specimens being stored long-term for potential use not outlined in the protocol are subject to University Policy Governing Tissue Sample Collection, Ownership, Usage, and Disposition within all UMMS Research Repositories.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Study Endpoints

This protocol will enroll patients with unresectable or metastatic HCC to cabozantinib in a Phase 1b/2 study design. The trial will be monitored using the Time-To-Event modification of the Continual Reassessment Method (TITE-CRM) (Cheung and Chappell 2000) (O'Quigley, Pepe et al. 1990). This method assumes a model for the time to occurrence of toxic responses as a function of the dose. The time-to-event modification allows information from all patients enrolled and treated (even those with only partial observation) to contribute information for calculating the dose-toxicity relationship. This method is flexible with regard to the number of patients treated at each dose level, patients may be continuously recruited throughout the trial, without recruitment pauses, as long as patients are assigned a dose deemed safe at the time of enrollment.

The primary endpoint is the occurrence/lack thereof of dose-limiting toxicity (defined in Section 5.1.2) during the first 29-days of therapy to identify the maximum tolerated dose/recommended Phase 2 dose (RP2D) in this patient population.

11.2 Sample Size and Accrual

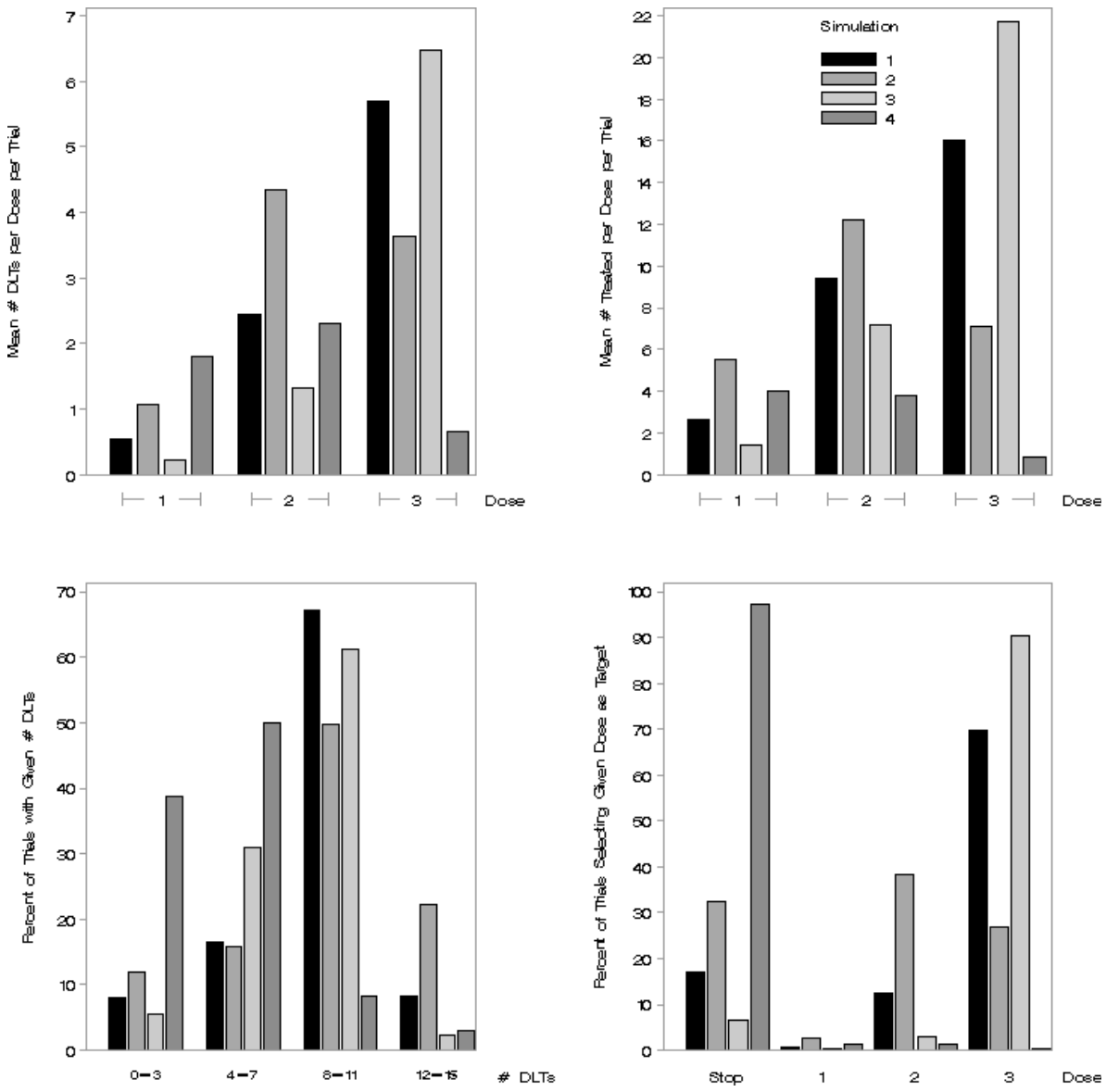
The study will enroll 32 patients for the estimates of the dose-toxicity function. Patients will be recruited as available and assigned to treatment according to the estimate probability of DLT as described above. No formal cohort size is required; however, at least two patients must be observed for their entire acute toxicity period (29 days) before dose escalation is allowed.

The operating characteristics of this trial design were evaluated through simulation, both near to and far from our expectations for toxicity. Table 7 lists our prior expectations for toxicity at each dose level and the simulated ‘truth’ for the four simulation scenarios. The simulation scenarios are: 1 – our prior expectations for toxicity are correct, 2 – our prior expectations moderately underestimate the true probability of toxicity at all dose levels, 3 – our prior expectations moderately overestimate the true probability for toxicity at all dose levels, and finally 4 – our prior expectation severely underestimated the true probability for toxicity. The MTD or RP2D is in gray; the dose level with the highest estimated probability of dose-limiting toxicity not exceeding 0.35.

Table 7. Operating Characteristics for Trial Schema					
Dose Level	**Expectation for probability of DLT**	**Scenario 1**	**Scenario 2**	**Scenario 3**	**Scenario 4**
0	20%	20%	20%	15%	45%
1*	27%	27%	35%	20%	60%
2	35%	35%	50%	30%	75%
Other Variables		**Scenario 1**	**Scenario 2**	**Scenario 3**	
Probability of early termination (PET)		17%	32%	7%	
Expected number (EN) of patients treated at MTD		16	12	22	
Probability of selecting correct dose level as MTD		70%	40%	90%	

**starting dose level*

The following figure displays the operating characteristics for this trial design under the four scenarios. The simulations indicate that this design does a good job of choosing the MTD or RP2D and treats a majority of patient at that dose level under scenarios both near to and far from expectations. The trial also stops early and protects the patient from the possibility of unjustifiable probability of DLT when the reality of the probability of DLT is moderately to severely higher than what we expect.



11.3 Dose Allocation

The dose level for each patient treated on this trial will be determined by the study statistician based upon selecting the dose level with the highest estimated probability of dose-limiting toxicity not to exceed or threshold of 35%, based upon our prior expectation and accumulating trial data; subject to the following constraints:

- The 1st and 2nd patients will be assigned to receive dose level 1
- Intra-subject dose escalation is not permitted
- The dose may be escalated only 1 dose level between adjacently accrued and treated patients. Dose de-escalated between adjacently accrued and treated patients is not restricted.
- At a minimum two patients at a given dose level are required to be completely observed for the DLT observation period (Cycle 1, days 1-28, D1C2 (day 29)) before escalation is allowed.
- Patients will be recruited as available and assigned to treatment according to the TiTE-CRM algorithm. No formal cohort sizes or accrual rate limits are required.

11.4 Data Analyses Plans

The TiTE-CRM estimates for the probability of DLT will be reported with 95% Bayesian Credible intervals, once the 32nd evaluable patient has completed the DLT observation period. The MTD/RP2D will be determined at that time as the dose level with the highest probability of DLT not exceeding 35%.

We will record ORR as a yes/no outcome for each patient for the period of active study treatment and report the estimate and exact 95% binomial confidence intervals. We will estimate PFS and OS using the product-limit method of Kaplan and Meier. Follow-up time will be defined as time from date of first study treatment until the date of radiological or clinical progression (leading to withdrawal from the study), or death from any cause, whichever comes first for PFS and for only death from any cause for OS. For patients without events, we will censor the follow-up time at the date of last disease evaluation at the time of analysis. We will report estimates for the median and 75th percentiles with 95% confidence intervals. We will summarize additional safety data (e.g., laboratory safety parameters, vital signs, concomitant medications and new physical examination findings) descriptively by reporting counts and percentages, with exact binomial confidence intervals where appropriate. ORR will be determined as per the RECISTv1.1 guidelines. We will report adverse events per the NCI CTCAE v5.0.

12.0 ADMINISTRATIVE PROCEDURES

12.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and be consistent with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH), WHO and any local directives.

The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.

12.2 Data Management

All information will be recorded locally and entered into Case Report Forms (CRFs) on the web-based electronic data capture (EDC) system of the University of Michigan. Online access will be provided to each site by the Coordinating Center.

CRFs will be reviewed and source verified by the multi-site project manager (MSPM) during annual monitoring visits and prior to and between visits. Discrepant, unusual and incomplete data will be queried by the MSPM. The investigator or study coordinator will be responsible for providing resolutions to the data queries, as appropriate. The investigator must ensure that all data queries are dealt with promptly.

The data submission schedule is as follows:

- At the time of enrollment
    - Subject entry into the EDC
- Subject Status
- Demographics
- During study participation
    - All data should be entered online within 10 business days of data acquisition. *[Information on dose limiting toxicity events must be entered within one business day.]* Information on Serious Adverse Events must be entered within the reporting timeframe specified in Section 8.4 of the protocol.

All study information should be recorded in an appropriate source document (e.g. clinic chart).

12.3 Record Retention

The Investigators must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, whichever is longer.

13.0 DATA AND SAFETY MONITORING

This study will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan, with oversight by the Rogel Cancer Center Data and Safety Monitoring Committee (DSMC).

The Sponsor-Investigator (S-I)/Study Principal Investigator will provide ongoing monitoring of data and patient safety in this trial and conduct regular data review with participating sites.

The Sponsor-Investigator (S-I)/Study Principal Investigator and/or the Project Manager/Delegate will review data and patient safety issues with participating sites in a **monthly** meeting. Depending on the protocol activity, the meeting cadence may be more frequent. This data review meeting may be achieved via a teleconference or another similar mechanism to discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (SAE reporting, unanticipated problems)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Participating sites are required to ensure all pertinent data for the review period are available in the database at the time of the discussion.

Participating sites unable to participate in the data review meeting are required to provide written confirmation that their site has reviewed the relevant data and patient safety issues for the review period and their site's data are in alignment with the data reported in the database. Written confirmation is to be provided to the Project Manager/Delegate within the timeline requested to retain compliance with monitoring timelines.

Documentation of the teleconference or alternate mechanism utilized to review items above is to be retained in the Trial Master File.

The Project Manager/Delegate is responsible for collating the data from all participating sites and completing the Protocol Specific Data and Safety Monitoring Report (DSMR) form to document the data review meeting discussion.

The DSMR will be signed by the Sponsor-Investigator (S-I)/Study Principal Investigator or designated Co-Investigator and submitted to the DSMC on a **monthly** basis for independent review.

14.0 QUALITY ASSURANCE AND AUDITS

The Data and Safety Monitoring Committee can request a 'for cause' quality assurance audit of the trial if the committee identifies a need for a more rigorous evaluation of study-related issues.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the Coordinating Center that such a request has been made.

15.0 CLINICAL MONITORING PROCEDURES

Clinical studies coordinated by The University of Michigan Rogel Cancer Center must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

This study will be monitored by a representative of the Coordinating Center of the Rogel Cancer Center. Monitoring visits will be made during the conduct of the study and at study close-out.

Prior to subject recruitment, a participating site will undergo site initiation meeting to be conducted by the Coordinating Center. This will be done as an actual site visit; teleconference, videoconference, or web-based meeting after the site has been given access to the study database and assembled a study reference binder. The site's principal investigator and his study staff should make every effort in attending the site initiation meeting. Study–related questions or issues identified during the site initiation meeting will be followed-up by the appropriate Rogel Cancer Center personnel until they have been answered and resolved.

Monitoring of this study will include both 'Centralized Monitoring', the review of source documents at the Coordinating Center and 'On-site Monitoring', an actual site visit. The first 'Centralized' visit should occur after the first subject enrolled completes [first treatment cycle/course]. The study site will send the de-identified source documents to the Coordinating Center for monitoring. 'Centralized' monitoring may be requested by the Coordinating Center if an amendment requires changes to the protocol procedures. The site will send in pertinent de-identified source documents, as defined by the Coordinating Center for monitoring.

The first annual 'On-site' monitoring visit should occur after the first five study participants are enrolled or twelve months after a study opens, whichever occurs first. The annual visit may be conducted as a 'Centralized' visit if less than three subjects have enrolled at the study site. The type of visit is at the discretion of the Coordinating Center. At a minimum, a routine monitoring visit will be done at least once a year, or once during the course of the study if the study duration is less than 12 months. The purpose of these visits is to verify:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Proper storage, dispensing and inventory of study medication
- Compliance with regulations

During a monitoring visit to a site, access to relevant hospital and clinical records must be given by the site investigator to the Coordinating Center representative conducting the monitoring visit to verify consistency of data collected on the CRFs with the original source data. While most patient cases will be selected from patients accrued since the previous monitoring visit, any patient case has the potential for review. At least one or more unannounced cases will be reviewed, if the total accruals warrant selection of unannounced cases.

The Coordinating Center expects the relevant investigational staff to be available to facilitate the conduct of the visit, that source documents are available at the time of the visit, and that a suitable environment will be provided for review of study-related documents. Any issues identified during these visits will be communicated to the site and are expected to be resolved by the site in a timely manner. For review of study-related documents at the Coordinating Center, the site will be required to ship or fax documents to be reviewed.

Participating site will also undergo a site close-out upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and that the site Investigator is aware of his/her ongoing responsibilities. In general, a site close-out is conducted during a site visit; however, site close-out can occur without a site visit.

16.0 REFERENCES

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17.0 APPENDICES

Appendix I	ECOG Performance Status
Appendix II	Child-Pugh Status
Appendix III	List of Strong Inhibitors and Inducers of CYP3A4
Appendix IV	Investigator's Statement

Appendix I ECOG Performance Status

	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Source: Eastern Cooperative Oncology Group

Appendix II Child-Pugh Score

Measure	1 point	2 points	3 points
Total Bilirubin (mg/dL)	<2	2-3	>3
Serum Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin Time • **PT >ULN (sec)** • **INR**	 1-3 <1.7	 4-6 1.7-2.3	 >6 >2.3
Ascites	Absent	Slight	Moderate to Severe
Hepatic Encephalopathy	None	Grade 1-2 (or suppressed with medication)	Grade 3-4 (or refractory)

Source: R.N.H. Pugh, I.M. Murray-Lyon, J.L. Dawson, M.C. Pietroni, Roger Williams. Transection of the esophagus for bleeding esophageal varices. British Journal of Surgery. Volume 60. Issue 8, pages 646-649, August 1973

Encephalopathy grades:
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

Appendix III List of Strong Inhibitors and Inducers of CYP3A4

Strong Inhibitors

Clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, grapefruit/grapefruit juice, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir.

Strong Inducers

Rifampin, carbamazepine, oxcarbazepine, nevirapine, fosphenytoin, pentobarbital, phenobarbital, , phenytoin, primidone, enzalutamide, lumacaftor, St John's Wort, mitotane, apalutamide, rimexolone, rifaximin, and rifamycin.

Appendix IV Investigator's Statement

1. I have carefully read this protocol entitled "Phase 1/2 Trial to Evaluate Cabozantinib in Patients with Advanced Hepatocellular Carcinoma with Child Pugh Class B Cirrhosis after First-Line Therapy", **Version 08/19/2020** and agree that it contains all the necessary information required to conduct the study. I agree to conduct the study as outlined in the protocol.

2. I agree to conduct this study according to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the principles of Good Clinical Practice (GCP) as described in 21 Code of Federal Regulations (CFR) and any applicable local requirements.

3. I understand that this trial and any subsequent changes to the trial will not be initiated without approval of the appropriate Institutional Review Board, and that all administrative requirements of the governing body of the institution will be complied with fully.

4. Informed written consent will be obtained from all participating patients in accordance with institutional and Food and Drug Administration (FDA) requirements as specified in Title 21, CFR, Part 50.

5. I understand that my signature on the electronic Case Report Form (eCRF) indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.

6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from University of Michigan unless this requirement is superseded by the FDA.

Site PI Name: _____

Site Name: _____

Signature of Site PI: _____

Date of Signature: _______________