NCT03213626


# A phase II trial of cabozantinib and erlotinib for patients with EGFR and c-Met co-expressing metastatic pancreatic adenocarcinoma

**PROTOCOL NUMBER:** IUSCC-0597

**STUDY DRUGS:** Cabozantinib (XL184)
Erlotinib

**IND NUMBER:** 134512

**SPONSOR:** IUSCC

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**SUPPORT PROVIDED BY:** IUSCC & Exelixis (cabozantinib)

**VERSION DATE:** 26 March 2019

# SYNOPSIS

## TITLE

A phase II trial of cabozantinib and erlotinib for patients with EGFR and c-Met co-expressing metastatic pancreatic adenocarcinoma

**PROTOCOL NUMBER:** IUSCC-0597

## CLINICAL PHASE

Phase II

## RATIONALE

This study is a trial based on the work of Dr. Murray Korc in the IUSCC, and is intended to be a key part of a SPORE grant for pancreatic cancer. The study looks at a novel combination of targeted agents in a biomarker-selected population of patients with pancreatic cancer, a group for whom new therapeutic options is desperately needed.

## OBJECTIVES

Primary:

- To demonstrate a radiographic response rate of 15% or greater for the combination in a selected population

Secondary:

- To estimate progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), overall survival (OS)
- To assess safety and tolerability of this combination in the target patient population

Correlative:

The following tests will be performed on blood and tumor tissue samples collected during this trial to correlate with PFS and OS:

- c-Met and EGFR mRNA by RT-qPCR
- plasma HGF and soluble Met receptor
- c-Met and EGFR phosphoprotein levels by IHC
- KRAS mutation status

## STUDY DESIGN

This is an open-label, single arm, phase II trial.

## NUMBER OF SUBJECTS

Approximately 37-40 subjects will be enrolled on this trial.

## TARGET POPULATION

1. Adenocarcinoma of the pancreas (or recurrence of previously resected disease) with metastatic disease;
2. EGFR and c-Met overexpressed in tumor as determined by immunohistochemistry (IHC) test score of 2+ for both markers;
3. Radiographic progression on one prior combination regimen for locally advanced or metastatic disease.

## ESTIMATED LENGTH OF SUBJECT PARTICIPATION

Subjects may continue to receive study treatment until they experience unacceptable drug-related toxicity, disease progression or subject withdrawal for any reason including investigator assessment that the risk:benefit ratio is no longer favorable. Subjects will be followed until death or two years (median follow-up of 8 months).

## ESTIMATED STUDY DATES

09/2017 (first study screening visit) to 12/2020 (last study follow-up visit)

## INVESTIGATIONAL REGIMEN DOSE/ROUTE/DURATION

Patients who meet the eligibility criteria will be treated with cabozantinib orally at 40 mg daily and erlotinib orally at 100 mg daily without breaks.

Cabozantinib is supplied as 20-mg tablets; Erlotinib is supplied as 25-mg, 100-mg, and 150-mg tablets.

## SAFETY ASSESSMENTS

Safety will be monitored on an ongoing basis. Laboratory testing (chemistry, hematology tests) will be performed every 2 weeks for the first 8 weeks followed by assessments every 4 weeks. Other safety evaluations including EKGs, urinalysis, coagulation and thyroid function studies will be performed at regular intervals.

Adverse event seriousness, severity grade, and relationship to study treatment will be assessed by the investigator. Severity grade will be defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

## TUMOR ASSESSMENTS

Tumors will be assessed by contrast enhanced CT or MRI every 8 weeks.

Pre-treatment tissue will be obtained via archival tissue collection. All tumor tissue from eligible patients will be utilized for the correlative studies which are outlined in this trial.

## BIOMARKER ASSESSMENTS

1. c-MET and EGFR mRNA by qPCR
2. plasma HGF and soluble c-Met receptor
3. c-Met and EGFR phosphoprotein levels by IHC
4. KRAS mutation status

## STATISTICAL METHODS

The optimal two-stage design to test the null hypothesis that $P \leq 0.025$ versus the alternative that $P \geq 0.150$ has an expected sample size of 17.32 and a probability of early termination of 0.757. If the drug is actually not effective, there is a 0.045 probability of concluding that it is (the target for this

value was 0.050). If the drug is actually effective, there is a 0.198 probability of concluding that it is not (the target for this value was 0.200). After testing the drug on 11 patients in the first stage, the trial will be terminated if 0 respond. If the trial goes on to the second stage, a total of 37 patients will be studied. If the total number responding is less than or equal to 2, the combination is rejected.

ORR and DCR will be estimated with 95% exact binomial confidence intervals. PFS will be estimated using a 95% confidence interval based on the exponential distribution. Safety and tolerability data will be tabulated. For biomarkers, baseline levels and changes over time will be correlated with PFS using Cox proportional hazards regression.

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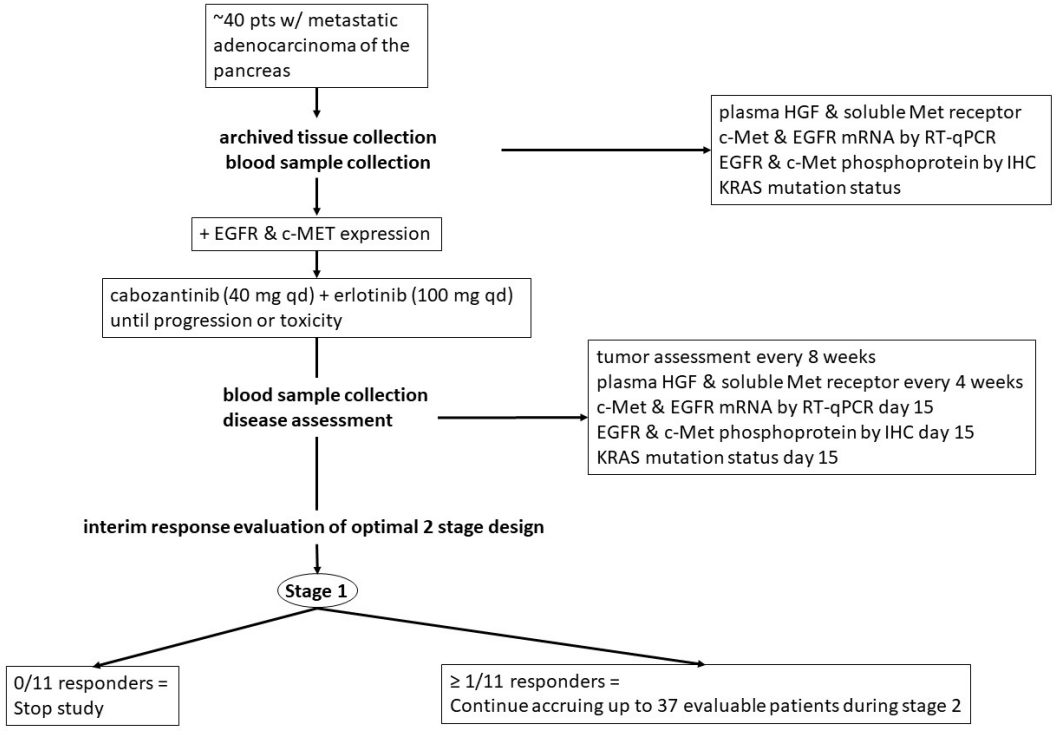
| LIST OF ABBREVIATIONS | |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| ASCO | American Society of Clinical Oncology |
| AST | aspartate aminotransferase |
| AUC | area under the plasma drug concentration time curve |
| BP | blood pressure |
| BUN | blood urea nitrogen |
| CHF | congestive heart failure |
| CrCl | creatinine clearance |
| CRF | case report form |
| CRPC | castration-resistant prostate cancer |
| CT | computerized tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | cytochrome P450 |
| DBP | diastolic blood pressure |
| DCR | disease control rate |
| DLT | dose-limiting toxicity |
| DVT | deep vein thrombosis |
| EC | ethics committee |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EKG | electrocardiogram |
| ESC | Exelixis Safety Committee |
| ESMO | European Society of Medical Oncology |
| ESR | erythrocyte sedimentation rate |
| FDA | Food and Drug Administration |
| FSH | follicle-stimulating hormone |
| GABA | γ-aminobutyric acid |
| GCP | Good Clinical Practice |
| GI | gastrointestinal |
| GGT | γ-glutamyl transferase |
| GnRH | gonadotropin-releasing hormone |
| ICH | International Conference on Harmonisation |
| IME | important medical event |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |

| | |
|---|---|
| IUSCC | Indiana University Simon Cancer Center |
| LDH | lactate dehydrogenase |
| LFT | liver function test |
| LHRH | luteinizing hormone-releasing hormone |
| LMWH | low molecular weight heparin |
| LLN | lower limit of normal |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | myocardial infarction |
| MRI | magnetic resonance imaging |
| MTC | medullary thyroid cancer |
| NCI | National Cancer Institute |
| NSAID | non-steroidal anti-inflammatory drug |
| NSCLC | non-small cell lung cancer |
| NYHA | New York Heart Association |
| ORR | objective response rate |
| PD | progressive disease |
| PDAC | pancreatic ductal adenocarcinoma |
| PE | pulmonary embolism |
| PI | principal investigator |
| PFS | progression-free survival |
| PPES | palmar-plantar erythrodysesthesia |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| qd | once daily |
| ONJ | osteonecrosis of the jaw |
| QTc | corrected QT interval |
| QTcF | QTc calculated by the Friderica formula |
| RBC | red blood cell |
| RPLS | reversible posterior leukoencephalopathy syndrome |
| RT-qPCR | reverse-transcriptase quantitative PCR |
| SAE | serious adverse event |
| SBP | systolic blood pressure |
| TCGA | The Cancer Genome Atlas |
| TFT | thyroid function test |
| TIA | transient ischemic attack |
| TSH | thyroid stimulating hormone |
| ULN | upper limit of normal |
| UPCR | urine protein/urine creatinine ratio |

| | |
|---|---|
| VEGF(R) | vascular endothelial growth factor (receptor) |

# 1 SCHEMA



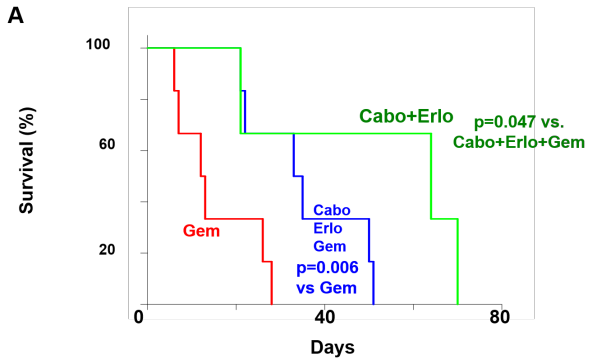

# 2 BACKGROUND AND RATIONALE

## 2.1 Background

Pancreatic ductal adenocarcinoma (PDAC) is a treatment-recalcitrant cancer with an overall 5-year survival rate of 7%. Metastatic is even more lethal, and therapeutic options remain limited. Based on a randomized study, the EGFR kinase inhibitor erlotinib appeared to have modest activity[1] and was approved by the FDA. Importantly, in a subset of patients who developed significant rash, there appeared to be a substantial survival benefit compared to either placebo treated patients or erlotinib treated patients who did not experience rash. EGFR overexpression relative to non-malignant pancreatic tissue is common in PDAC;[2] however, KRAS mutation is also nearly universal,[3] and may mediate resistance to EGFR therapy.[4] Importantly, recent evidence with mouse models underscores the requirement for EGFR signaling in order to allow oncogenic KRAS to drive pancreatic neoplastic transformation and progression.[5]

Another cell-surface signaling pathway that has been shown to have preclinical activity in pancreatic cancer models is the HGF/c-Met signaling axis. The c-Met receptor, as is the case for EGFR, is overexpressed in a majority of PDACs.[6] Based on previous studies, a substantial fraction of PDACs co-overexpress these two receptors and their ligands.[7-9] As early as 2000 it was noted that cross-talk exists between the two pathways,[7-9] and that the two pathways can synergize in terms of activation of downstream pathways. Importantly, investigators at our institution and others have documented heterodimerization of c-Met and EGFR subunits. These heterodimers result in more signaling that enhances pancreatic cancer cell invasion and p-AKT signaling, (Murray Korc, personal communication) even in the presence of mutated KRAS. This co-receptor signaling suggests that inhibition of both receptors simultaneously may be required for anti-tumor activity, and also suggests a target population of tumors overexpressing both molecules. Based on these preclinical findings, we propose a trial to test this hypothesis in patients with metastatic PDAC (mPDAC) that co-expresses c-Met and EGFR.

**Figure 1.** Cabo+Erlo is More Effective than Cabo+ Erlo+Gem in KPC Mice




The combination of cabozantinib and erlotinib has been studied previously in non-small cell lung cancer (NSCLC). The combination was considered tolerable, with adverse events consisting primarily of diarrhea (29% grade 3) and rash (6% grade 3).[10]

## 2.2 Rationale

At present, the majority of fit patients with mPDAC are treated in the first-line with either FOLFIRINOX (leucovorin, fluorouracil [5-FU], irinotecan and oxaliplatin) or gemcitabine and nab-paclitaxel. Recently, MM-398 (irinotecan liposome injection) was approved in combination with 5-FU for patients failing initial gemcitabine-based chemotherapy,[11] but no regimen has been adequately studied to be considered a standard of care for patients who have failed front-line treatment, and patients often have difficulty tolerating further combination chemotherapy after progressing on an intensive combination regimen, with hematologic toxicity and neuropathy as particular problems. As such, there remains a substantial unmet need for second-line therapy of metastatic PDAC. Based on this unmet need and the preclinical data above, we propose a phase II trial of the combination of erlotinib and cabozantinib for patients with EGFR+/c-Met+

metastatic pancreatic cancer who have been treated with and progressed on (or within 3 months of stopping) front-line treatment for advanced disease. While The Cancer Genome Atlas (TCGA) data suggest that concomitant overexpression of EGFR and c-Met occurs in 3% of PDAC patients, based on our unpublished results using reverse-transcriptase quantitative PCR (RT-qPCR), we have found that ~30% of these patients have increased levels of both EGFR and c-Met.

# 3 STUDY OBJECTIVES AND DESIGN

## 3.1 Study Objectives

### 3.1.1 Primary Objective

The primary objective of this trial is to demonstrate a radiographic response rate of 15% or greater for the combination in a selected population.

### 3.1.2 Secondary Objectives

The secondary objectives of this trial are:

- To estimate progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), overall survival (OS); and
- To assess safety and tolerability of this combination in the target patient population.

### 3.1.3 Correlative Objectives

The following tests will be performed on blood and tumor tissue samples collected during this trial to correlate with PFS and OS:

- c-Met and EGFR mRNA by RT-qPCR
- plasma HGF and soluble Met receptor
- c-Met and EGFR phosphoprotein levels by IHC
- KRAS mutation status

## 3.2 Study Design

This is an open-label, single arm, phase II trial.

Safety will be monitored on an ongoing basis. Laboratory testing (chemistry, hematology tests) will be performed every 2 weeks for the first 8 weeks followed by assessments every 4 weeks. Other safety evaluations including EKGs, urinalysis, coagulation and thyroid function studies will be performed at regular intervals.

Adverse event seriousness, severity grade, and relationship to study treatment will be assessed by the investigator. Severity grade will be defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Each subject's course will consist of three periods:

- A Pre-Treatment Period in which subjects are consented and undergo screening assessments to be qualified for the study (Section 6.2);
- A Treatment Period in which subjects receive study treatment and undergo study assessments (Section 6.3);
- A Post-Treatment Period in which subjects no longer receive study treatment but undergo follow-up study assessments and contacts (Section 6.4).

### 3.3 Treatment Assignment

It is the responsibility of the investigator to assign a subject number before treating each subject with cabozantinib and erlotinib.

### 3.4 Blinding and randomization

This is a non-randomized trial.

### 3.5 Study Sites

This study will be conducted at the Indiana University Melvin and Bren Simon Cancer Center/Indiana University Health Hospital.

### 3.6 Withdrawals

Subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. The investigator may withdraw a subject from study treatment or from the study if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

In addition, any of the following conditions require discontinuation of the subject from study treatment:

- An adverse event or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from study treatment;
- The investigator believes it is not in the best interest of the subject to continue on study
- Specific conditions described in the Sections 4.4 Warnings and Precautions and Guidelines for the Management of Adverse Events;
- Necessity for treatment with other anticancer treatment prohibited by protocol;
- 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;
- Women who become pregnant or are breastfeeding;

- If the subject does not recover from his or her toxicities to tolerable Grade ≤ 2 within 6 weeks, the subject will have study treatment discontinued 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 and with agreement of the sponsor-investigator;
- 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;
- Progressive disease (PD) or the subject no longer experiences clinical benefit as determined by the investigator

# 4 TREATMENTS

## 4.1 Investigational Treatment

### 4.1.1 Cabozantinib Tablets

Exelixis internal number: XL184

Chemical name: *N*-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-*N*'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate

Cabozantinib tablets are supplied as film coated tablets containing cabozantinib malate equivalent to 20 mg or 60 mg of cabozantinib and contain microcrystalline cellulose, lactose anhydrous, hydoxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry® yellow. All tablet strengths are prepared from a common blend and are distinguished by shape. The 20 mg tablets are round and the 60 mg tablets are oval. The components of the tablets are listed in Table 4-1. Details regarding the pharmacology, nonclinical toxicology and clinical experience can be found in the Investigator's Brochure for cabozantinib.

**Table 4-1: Cabozantinib Tablet Components and Composition**

| Ingredient | Function | % w/w |
|---|---|---|
| Cabozantinib malate (25% drug load as cabozantinib) | Active Ingredient | 31.7 |
| Microcrystalline Cellulose (Avicel PH-102) | Filler | 38.9 |
| Lactose Anhydrous (60M) | Filler | 19.4 |
| Hydroxypropyl Cellulose (EXF) | Binder | 3.0 |
| Croscarmellose Sodium (Ac-Di-Sol) | Disenegrant | 6.0 |
| Colloidal Silicon Dioxide, | Glidant | 0.3 |
| Magnesium Stearate | Lubricant | 0.75 |
| Opadry Yellow Film Coating which includes:<br>- HPMC 2910/Hypromellose 6 cp<br>- Titanium dioxide<br>- Triacetin<br>- Iron Oxide Yellow | Film Coating | 4.00 |

### 4.1.2 Erlotinib Tablets

Trade name: tarceva

Chemical name: N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine

Erlotinib tablets for oral administration are available in three dosage strengths containing erlotinib hydrochloride (27.3 mg, 109.3 mg, and 163.9 mg) equivalent to 25 mg, 100 mg, and 150 mg erlotininb and the following inactive ingredients: lactose monohydrate, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and titanium dioxide. The tablets which are round, biconvex face and straight sides, also contain trace amounts of color additives, including FD&C Yellow #6 (25 mg only) for product identification.

Details regarding the pharmacology, nonclinical toxicology and clinical experience can be found in the Package Insert for erlotinib.

## 4.2 Composition, Formulation, and Storage

All study medication will be stored as described in the pharmacy manual and inventoried in accordance with applicable state and federal regulations.

### 4.3 Dose, Schedule and Route

Subjects will receive cabozantinib orally at a dose of 40 mg once daily (qd), and erlotinib orally at a dose of 100 mg qd.

Both study medications must be taken on an empty stomach. Subjects will be instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib and erlotinib. Subjects should be instructed to take their study medications 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 and erlotinib tablets should be swallowed whole with at least 8 ounces of water. The tablets should not be crushed. Grapefruit, grapefruit juice, and Seville oranges and their products should be avoided by subjects taking cabozantinib.

Avoid concomitant use of erlotinib with proton pump inhibitors if possible. If concomitant use of an $H_2$-receptor antagonist such as ranitidine is required, erlotinib should be taken 10 hours after the $H_2$-receptor antagonist dosing and at least 2 hours before the next dose of the $H_2$-receptor antagonist.

If concomitant antacid use is necessary, the antacid dose and erlotinib dose should be separated by several hours.

In all subjects, dose reductions and delays to manage toxicity are allowed under the guidelines in Section 4.3.1 below.

#### 4.3.1 Dose Modifications, Interruptions, and Discontinuation

Subjects will be monitored for adverse events (AEs) from the time of first study intervention (i.e., biopsy, if needed, or treatment, whichever comes first) through their last follow-up visit (i.e., 30 days after the date of the last dose of study treatment). Subjects will be instructed to notify their physician immediately at the onset of any AE. Causality assessment of AEs will be determined by the investigator. AE severity will be graded by the investigator in accordance with CTCAE v.4.03.

The following should be taken into consideration in decisions regarding dose modifications (reductions or interruption):

- As a general approach all AEs should be managed with supportive care at the earliest signs of toxicity considered related to the study treatment. Should this be ineffective, dose interruptions and/or reductions should be considered to prevent worsening of toxicity.
- Dose modification criteria are shown in Table 4-3.
- Dose interruptions and/or reductions should be implemented for unacceptable toxicity. Doses may be modified at any time while a subject is on treatment.
- The assigned starting dose for cabozantinib is 40 mg/day, and the assigned starting dose for erlotinib is 100 mg/day. One dose reduction level of cabozantinib and one dose reduction level of erlotinib are permitted (see Table 4-2).
- Dose reductions or interruptions may also occur in the setting of lower grade toxicity than defined in Table 4-3 if the investigator feels it is in the interest of a subject's safety and will optimize drug tolerability.
- Interruption of treatment for treatment-related AEs may occur at any time per investigator discretion. If treatment is interrupted due to related AEs for more than 6 weeks, treatment should be discontinued 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.
- Dose interruptions for reason(s) other than related AEs (e.g., surgical procedures) can be longer than 6 weeks per the discretion of the investigator.
- Subjects may continue on only one study drug if the other drug must be stopped altogether and physician believes there is clinical benefit to staying that drug.

Guidelines for the management of specific AEs are provided in Section 4.4.1.

**Table 4-2: Dose Reductions of Cabozantinib and Erlotinib**

| **Assigned Starting Dose** | **First Dose Level Reduction** |
|---|---|
| 40-mg cabozantinib oral qd | 20-mg cabozantinib oral qd<br>(discontinue if this dose is not tolerated) |
| 100-mg erlotinib oral qd | 50-mg erlotinib oral qd (discontinue if this dose is not tolerated) |

See Section 4.5.5 for complete details regarding potential drug interactions.

**Table 4-3: Dose Modifications for Treatment-Related AEs for Cabozantinib and Erlotinib**

Dose modifications should be made to both cabozantinib and erlotinib for any overlapping treatment-related adverse events unless the investigator suspects one drug over another to be the cause of unacceptable toxicity. In this case, dose modifications may be made to one drug per the investigator's discretion. The most common overlapping toxicities are: diarrhea, fatigue, nausea, skin reactions and vomiting.

| CTCAE v.4.03 Grade | Recommended Guidelines for Management[a] |
|---|---|
| Grade 1 AEs | Add supportive care as indicated. Continue treatment at the current dose level if AE is manageable and tolerable. |
| Grade 2 AEs which are tolerable and are easily managed | Continue treatment at the current dose level with supportive care. |
| Grade 2 AEs which are **intolerable** and **cannot be adequately managed** | At the discretion of the investigator, treatment should be dose reduced or interrupted.<br>Note: It is recommended that dose holds be as brief as possible. |
| Grade 3 AEs (except clinically non-relevant laboratory abnormalities) | Treatment should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care.<br>Note: It is recommended that dose holds be as brief as possible. |
| Grade 4 AEs (except clinically non-relevant laboratory abnormalities) | Subjects should have treatment interrupted immediately. Discontinue treatment unless the following criteria are met:<br>• Subject is deriving clear clinical benefit as determined by the investigator and agreed by the sponsor-investigator<br>• Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care |

Note: The dose delay and modification criteria for specific medical conditions are provided in Section 4.3.1. For re-treatment criteria of study treatment after a dose hold see Section 4.3.2.

[a] Study treatment dose adjustment is only needed if the toxicity was deemed related to treatment or had an unclear relationship to treatment.

### 4.3.2 Dose Reinstitution and Reescalation

If the subject recovers from his or her toxicities to CTCAE v.4.03Grade ≤ 1 or to the baseline value (or lower) and the toxicity was unrelated to study treatment, then study treatment may be restarted with no change in dose.

If the subject recovers from his or her toxicities to Grade ≤ 1 or to the baseline value (or lower) the toxicity was deemed possibly related to study treatment, then study treatment may be restarted at a reduced dose (see Table 4-2 for the schedule of dose reductions).

Subjects receiving the lowest trial dose (cabozantinib = 20 mg/day; erlotinib = 50 mg/day) may be restarted at the same dose if deemed safe at the discretion of the investigator. Subjects unable to tolerate the lowest trial dose should discontinue study treatment.

Re-escalation to the previous dose, (but not higher than the trial dose [cabozantinib = 40 mg/day; erlotinib = 100 mg/day]) may be allowed at the discretion of the investigator and agreement of the PI for AEs which have resolved or recovered to Grade 1 (or baseline value) and deemed tolerable and easily managed by optimized supportive treatment. Dose re-escalation is not allowed for a drug-related dose reduction triggered by Grade 4 hematologic toxicities or by Grade 4 AEs affecting major organs (e.g., central nervous system, cardiac, hepatic, renal).

## 4.4 Warnings and Precautions and Guidelines for the Management of Adverse Events

The most frequent adverse events experienced by ≥ 20% of subjects were:

- Cabozantinib: diarrhea, fatigue, nausea, decreased appetite, vomiting, weight decreased, palmar-plantar erythrodysesthesia syndrome (PPES), constipation, hypertension, dysgeusia, dysphonia, and asthenia.
- Erlotinib: rash, diarrhea, anorexia, fatigue, dyspnea, cough, nausea, and vomiting.

Adverse events associated with laboratory abnormalities experienced by ≥ 5% of subjects include:

- Cabozantinib: anemia, AST increased, ALT increased, hypothyroidism, hypokalemia, hypomagnesemia, thrombocytopenia, hypocalcemia, hypophosphatemia, lipase increased, lactate dehydrogenase (LDH) increased, neutropenia, ALP increased, hyponatremia, and leukopenia. Mild to moderate QTc interval prolongation (10-15ms) has also been observed with a QT interval calculated by the Fridericia formula (QTcF) not exceeding 500 ms.

Subjects may also experience medically important but less frequent adverse events including:

- Cabozantinib: arterial and venous thrombotic AEs (e.g., deep vein thrombosis [DVT], pulmonary embolism [PE], transient ischemic attack [TIA], and myocardial infarction

[MI]), severe hemorrhagic events, proteinuria, wound healing complications, gastrointestinal [GI] perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistulae formation, osteonecrosis, and reverse posterior leukoencephalopathy syndrome (RPLS).

- Erlotinib: interstitial lung disease (ILD), renal failure, hepatoxicity with or without hepatic impairment, GI perforation, bullous and exfoliative skin disorders, MI/ischemia, cerebrovascular accident (CVA), microangiopathic hemolytic anemia with thrombocytopenia, ocular disorders, hemorrhage in patients taking warfarin, and embryo-fetal toxicity. Please refer to the package insert for more detailed information on managing these conditions.

Treatment should be permanently discontinued for the following adverse events:

- Cabozantinib: visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic events, nephrotic syndrome, malignant hypertension, hypertensive emergency, persistent uncontrolled hypertension despite optimal medical management, osteonecrosis of the jaw (ONJ), and serious and life-threatening RPLS.
- Erlotinib: ILD, severe hepatic toxicity (see Section 4.4.1.2), gastrointestinal perforation, severe bullous, blistering, or exfoliating skin conditions, and corneal perforation or severe ulceration.

The predicted effective plasma half-life of cabozantinib is 55 hours. Thus, when initiating therapy with cabozantinib, it will take most subjects 2 to 3 weeks to reach steady state. If AEs attributable to cabozantinib occur within the initial 3-week period of dosing, early intervention with dose modifications may be justified for AEs that, if worsened, could potentially be dangerous or debilitating, because without a dose adjustment, systemic exposure of cabozantinib might be expected to increase after the onset of the AE. Cabozantinib-related events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea and vomiting.

A population pharmacokinetic analysis in 591 patients receiving the single-agent erlotinib 2$^{nd}$/3$^{rd}$ line regimen showed a median half-life of 36.2 hours. Time to reach steady state plasma concentration would therefore be 7 to 8 days. No significant relationship of clearance to covariate of patient age, body weight, or gender were observed. Smokers had a 24% higher rate of erlotinib clearance. Similar results were observed in a population pharmoacokinetic analysis

conducted with 204 pancreatic cancer patients who receive erlotinib plus gemcitabine. Co-administration of gemcitabine had no effect on erlotinib plasma clearance. Rash and diarrhea, the most common adverse reactions with erlotinib, usually occur within one month of starting treatment.

### 4.4.1 Guidelines for Management of Potential Adverse Events

Please refer to the subsections below for specific guidelines regarding the following potential adverse events:

| | |
|---|---|
| Gastrointestinal disorders (diarrhea, nausea, decreased appetite, vomiting, constipation, stomatitis and abdominal pain) | Section 4.4.1.1<br>Table 4-4: Management of Treatment-Emergent Diarrhea |
| Hepatobiliary disorders (elevations of ALT, AST, bilirubin; hepatic failure, hepatorenal syndrome) | Section 4.4.1.2 |
| Hematological disorders (neutropenia, thrombocytopenia) | Section 4.4.1.3 |
| Fatigue, anorexia, and weight loss | Section 4.4.1.4 |
| Skin disorders (rash [blisters, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash], palmar-plantar erythrodysesthesia syndrome [PPES], pruritus, dry skin, erythema, pigmentary changes, alopecia) | Section 4.4.1.5<br>Table 4-5: Management of PPES |
| Wound healing and surgery | Section 4.4.1.6 |
| Hypertension | Section 4.4.1.7<br>Table 4-6: Management of Hypertension Related to Cabozantinib |
| Thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE], transient ischemic attack [TIA], myocardial infarction, ischemia, cerebrovascular accident) | Section 4.4.1.8 |
| Proteinuria | Section 4.4.1.9<br>Table 4-7: Manage of Proteinuria |
| Corrected QTc prolongation | Section 4.4.1.10 |
| Hypophosphatemia | Section 4.4.1.11 |
| Thyroid function disorders (changes in thyroid function tests, hypothyroidism) | Section 4.4.1.12 |
| Hemorrhagic events | Section 4.4.1.13 |
| GI perforation/fistula and non-GI fistula | Section 4.4.1.14 |
| Osteonecrosis of the jaw | Section 4.4.1.15 |
| Respiratory, thoracic and mediastinal disorders (cough, dyspnea, fistula formation, pneumonia, interstitial lung disease [ILD]) | Section 4.4.1.16 |
| Renal failure (hepatorenal syndrome, severe acute renal failure, renal insufficiency) | Section 4.4.1.17 |
| Ocular disorders (decrease tear production, abnormal eyelash growth, keratoconjunctivitis sicca, keratitis) | Section 4.4.1.18 |

#### 4.4.1.1 Gastrointestinal Disorders

The most common non-hepatobiliary GI AEs reported in clinical studies with cabozantinib regardless of causality are diarrhea, nausea, decreased appetite, vomiting, constipation, stomatitis and abdominal pain. Diarrhea, nausea, and vomiting were amongst the most common adverse reactions experienced by ≥ 20% of subjects who took erlotinib.

Diarrhea: Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements.

Guidelines for the evaluation and management of diarrhea are shown in Table 4-4.

Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, cabozantinib and erlotinib should be temporarily interrupted or dose reduced. When the diarrhea is controlled, retreatment with cabozantinib and erlotinib may be acceptable per investigator decision.

In addition, general supportive measures should be implemented such as continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol.

Recurrent or prolonged diarrhea can be associated with anal or perianal skin erosions which increase the risk for anal abscesses, fistulas, or proctitis. Good personal hygiene should be emphasized. Regular examinations of the perianal region should be performed whenever diarrhea has occurred during treatment with cabozantinib and erlotinib. Infections of the perianal region should be treated per local guidelines.

**Table 4-4: Management of Treatment-Emergent Diarrhea**

| CTCAE v.4.03 Grade | Action To Be Taken |
|---|---|
| Tolerable Grade 1-2 (duration < 48 h) | • Continue with study treatment and consider dose reduction<br>• Initiate treatment with an antidiarrheal agent (eg, loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day])<br>• Dietary modifications (eg, small lactose-free meals, bananas and rice)<br>• Intake of isotonic fluids (1-1.5 L/day)<br>• Re-assess after 24 hours:<br>o Diarrhea resolving to baseline bowel habits: gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 h diarrhea-free interval<br>o Diarrhea not resolving: Continue/resume antidiarrheal |
| Intolerable Grade 2, Grade 2 > 48 h, or ≥ Grade 3 | • Interrupt study treatment<br>• Ask subject to attend clinic<br>• Rule out infection (eg, stool sample for culture)<br>o Administer antibiotics as needed (eg, if fever or Grade 3-4 neutropenia persists > 24 h)<br>• Administer fluids (1-1.5 L/day orally or IV, as appropriate) for hydration or to correct electrolyte abnormalities<br>• For Grade 3-4 or complicated lower grade diarrhea consider hospitalization and IV hydration<br>• Re-assess after 24 h<br>o Diarrhea resolving to baseline bowel habits or Grade ≤ 1: consider restarting study treatment at reduced dose<br>o Diarrhea not resolving:<br>• Start and or continue antidiarrheal treatment (eg, loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day])<br>• Consider starting second line antidiarrheal or referral to gastroenterologist<br>o If severe diarrhea cannot be resolved with the measures listed above, discontinue treatment. |

#### 4.4.1.2 Hepatobiliary Disorders

Elevations of ALT, AST, and bilirubin have been observed during treatment with cabozantinib. Hepatic failure and hepatorenal syndrome, including fatal cases, can occur with erlotinib treatment in subjects with normal hepatic function; the risk of hapatic toxicity is increased in subjects with baseline hepatic impairment. Perform periodic liver testing (transaminases,

bilirubin, and alkaline phosphatase) during treatment. If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or bilirubin.

Subjects on this study may enter with increased ALT/AST serum levels up to 3 × ULN. Dose reductions of study treatment should be considered in any subject who develops drug-related grade 2 bilirubin lasting longer than 1 week. In subjects who develop doubling of ALT/AST elevations in combination with a bilirubin elevation > 2 × ULN without reasonable other explanation, drug-induced liver injury should be suspected and treatment interrupted. Reinstitution of study treatment after recovery of ALT, AST, and bilirubin to baseline level is at the discretion of the investigator.

Withhold and consider discontinuing erlotinib in subjects without pre-existing hepatic impairment for total bilirubin levels greater than 3 x the ULN or transaminases greater than 5 x the ULN. Withhold and consider discontinuing erlotinib in patients with pre-existing hepatic impairment or biliary obstruction for doubling of bilirubin or tripling of transaminases values over baseline. Discontinue erlotinib in subjects whose abnormal liver tests meeting the above criteria do not improve significantly or resolve within 3 weeks.

#### 4.4.1.3 Hematological Disorders

Hematological toxicities (i.e., neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be managed with dose interruptions and/or dose reductions. Use of granulocyte colony-stimulating factor support for neutrophil recovery is allowed per investigator discretion and in accordance with accepted guidelines after the first incidence of clinically relevant cytopenia.

Febrile neutropenia or evidence of infection associated with neutropenia should be treated appropriately and in a timely manner according to institutional guidelines.

Dose reductions or dose interruptions for anemia are not mandated but can be applied as clinically indicated. Supportive care such as red blood cell transfusions may be managed according to institutional guidelines.

#### 4.4.1.4 Fatigue, Anorexia, and Weight Loss

Fatigue has been reported during treatment with cabozantinib and erlotinib. Refer to Table 4-3 for general management guidelines.

Anorexia and weight loss should be managed in accordance to local standard of care including nutritional support. If fatigue, anorexia, or weight loss cannot be adequately managed, study treatment should be temporarily interrupted or dose reduced per Table 4-2 and Table 4-3.

#### 4.4.1.5 Skin Disorders

Palmar-plantar erythrodysesthesia syndrome (PPES; also known as hand-foot syndrome), skin rash (including blisters, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported in cabozantinib-treated subjects. Treatment guidelines for PPES related to study treatment are presented in Table 4-5.

Rash was amongst one of the most common adverse reactions experienced by ≥ 20% of subjects who took erlotinib. Grade 3-4 rash was reported in 5% of patients treated with erlotinib and gemcitabine as first-line treatment of pancreatic cancer. Rash includes PPES, acne, skin disorder, pigmentation disorder, erythema, skin ulcer, dermatitis exfoliative, rash popular, and skin desquamation. Bullous, blistering and exfoliative skin conditions, including cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, which in some cases were fatal, can occur with erlotinib treatment. Discontinue treatment in subjects who develop severe bullous, blistering or exfoliating conditions. Please refer to the guidelines for treatment-related rash (except for PPES which can be found in Table 4-5 below) in Table 4-3.

In the case of study treatment-related skin changes (e.g., rash, hand-foot syndrome), the investigator may request that additional assessments be conducted with the subject's consent. These assessments may include digital photographs of the skin changes and/or a biopsy of the affected skin and may be repeated until the skin changes resolve.

**Table 4-5: Management of Treatment-Emergent Hand-Foot Syndrome (PPES)**

| CTCAE v.4.03 Grade | Action To Be Taken |
|---|---|
| Grade 1 | Study treatment may be continued at the current dose if PPES is clinically insignificant and tolerable. Otherwise, study treatment should be reduced to the next lower dose level.[a] 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 | Study treatment may be continued if PPES is tolerated. Study treatment should be dose reduced or interrupted if PPES is intolerable. Continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily and add analgesics (e.g., non-steroidal anti-inflammatory drug (NSAID)s/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 study treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with clobetasol 0.05% cream 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. |

[a] Permitted dose levels are defined by individual protocols.

#### 4.4.1.6 Wound Healing and Surgery

Surgical and traumatic wounds must have completely healed before starting cabozantinib treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with cabozantinib. If possible, cabozantinib treatment should be stopped for at least 28 days prior to major surgery.

#### 4.4.1.7 Hypertension

Hypertension is a common class effect of drugs that inhibit VEGF pathways and has been reported among subjects treated with cabozantinib.

Treatment guidelines for hypertension deemed related to cabozantinib are presented in Table 4-6. Blood pressure should be monitored in a constant position at each visit (either sitting or supine). In general, subjects with known hypertension should be optimally managed before study entry. Decisions to decrease or hold the dose of study treatment must be based on blood pressure readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes after the first measurement. Other than for hypertension requiring immediate therapy, the presence of new or worsened hypertension should be confirmed at a second visit before taking therapeutic action. It is recommended that this second visit occurs within 1 week.

Treatment should be discontinued in subjects with hypertensive crises or hypertensive encephalopathy.

**Table 4-6: Management of Hypertension Related to Cabozantinib**

| Criteria for Dose Modifications | Treatment/Cabozantinib Dose Modification |
|---|---|
| **Subjects NOT receiving optimized anti-hypertensive therapy** | |
| > 150 mm Hg (systolic)[a] and < 160 mm Hg<br>OR<br>> 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.<br>• Reduce study 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<br>• If subject is symptomatic interrupt study treatment |
| ≥ 160 mm Hg (systolic)<br>OR<br>≥ 110 mm Hg (diastolic) | • Reduce cabozantinib by one dose level[b] or interrupt study treatment per investigator discretion<br>• 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, study treatment should be dose reduced further or interrupted<br>• Study 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<br>• Re-start study 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[c] | • Discontinue study treatment |

[a] The investigator may decide to initiate or adjust antihypertensive treatment at a lower threshold than systolic BP >150 or diastolic BP >100 based on their clinical judgment and assessment of the individual subject.
[b] Permitted dose levels are defined by individual protocols.
[c] Hypertensive emergency is defined as uncontrolled elevated blood pressure with clinical evidence of progressive or impending end-organ damage (eg, myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, kidney damage).

#### 4.4.1.8 Thromboembolic Events

Thromboembolic complications are frequent in cancer patients due to procoagulant changes induced by the malignancy or anticancer therapy including inhibitors of VEGF pathways. Deep vein thrombosis and PE have been observed in clinical studies with cabozantinib; including fatal

events (please refer to the Investigator's Brochure). Subjects who develop a PE or DVT should have treatment held until therapeutic anticoagulation with heparins (e.g., low molecular weight heparin [LMWH]) is established. LMWH are the preferred management for thrombotic events, warfarin is not recommended although is allowed at investigator discretion. Treatment may be resumed in subjects who are stable and have uncomplicated PE or DVT and are deriving clinical benefit from treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the investigator/PI. During anticoagulation treatment, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding which may require additional or more frequent laboratory tests in accordance to institutional guidelines. If there are any signs of clinically significant bleedings, treatment should be permanently discontinued.

Arterial thrombotic events have been observed in studies with cabozantinib (e.g., transient ischemic attack, myocardial infarction) and erlotinib (e.g., myocardial infarction/ischemia, cerebrovascular accident). Treatment should be discontinued in subjects who develop an acute myocardial infarction, cerebral infarction or any other clinically relevant arterial thromboembolic complication.

#### 4.4.1.9 Proteinuria

Proteinuria is an anticipated AE with the inhibition of VEGF pathways and has been observed in cabozantinib clinical studies, and nephrotic syndrome has been reported with cabozantinib and other inhibitors of VEGF pathways. Management guidelines are provided in Table 4-7.

Treatment should be permanently discontinued in subjects who develop nephrotic syndrome (proteinuria > 3.5 grams per day in combination with hypoalbuminemia and peripheral edema [hyperlipidemia and thrombotic disease may also be present]) or any other relevant renal disease.

**Table 4-7: Management of Treatment-emergent Proteinuria**

| Severity of Proteinuria (UPCR) | Management of 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-hour protein assessment within 7 days<br>• No change in cabozantinib treatment required if UPCR ≤ 2 mg/mg or urine protein ≤ 2 g/24 hours on 24-hour urine collection.<br>• Dose reduce or interrupt cabozantinib treatment if UPCR > 2 mg/mg on repeat UPCR testing or urine protein > 2 g/24 hours on 24-hour urine collection. Continue cabozantinib on a reduced dose if UPCR decreases to < 2 mg/mg. Consider holding 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 hold unless otherwise approved by PI.<br>• 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. |
| ≥ 3.5 mg/mg (≥ 395.9 mg/mmol) | • Hold cabozantinib treatment pending repeat UPCR within 7 days and/or 24-hour urine protein.<br>• If ≥ 3.5 mg/mg on repeat UPCR, continue to hold cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to < 2 mg/mg, restart cabozantinib treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to < 1 mg/mg. 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 all study treatment |

#### 4.4.1.10 Corrected QTc Prolongation

The effect of orally administered cabozantinib 140 mg qd on QTc interval was evaluated in a placebo-controlled study in subjects with MTC. A mean increase in QTcF of 10-15 ms was observed after 4 weeks after initiating cabozantinib treatment. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib-treated subjects in this study had a QTcF > 500 ms.

Cabozantinib should be used with caution in subjects with QT prolongation risk, a history of QT interval prolongation, or who are taking antiarrhythmics or drugs known to prolong the QT interval. Concomitant treatment with strong CYP3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be avoided.

If at any time on study there is an increase in QTcF to an absolute value > 500 ms or an increase of > 60 ms above baseline, two additional ECGs must be performed with intervals not less than 3 min apart within 30 min after the initial ECG.

If the average QTcF from the three ECGs is > 500 ms or increased by > 60 ms above baseline, the following actions must be taken:

- Withhold study treatment
- Immediately notify the PI
- Hospitalize symptomatic subjects (e.g., with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management
- Consider cardiology consultation for asymptomatic subjects for evaluation and management
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org)

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation and symptoms have resolved. Study treatment may be restarted at a reduced dose level if all of the following conditions are met:

- Symptoms are determined to be unrelated to the QT interval prolongation
- The QTcF value > 500 ms or increase of > 60 ms above baseline is not confirmed according to protocol procedures
- Study treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 msec or return to ≤ 60 ms above baseline.
- QT prolongation can be unequivocally associated with an event other than cabozantinib administration and is treatable/has been resolved
- PI has reviewed all available information and has agreed to the continuation of study treatment

Following reinitiation of study treatment, ECGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then according to the protocol-defined time points.

All study treatment must be permanently discontinued if either of the following applies:

- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation
- Recurrence of QTcF prolongation (confirmed by ECG lab) after reinitiation of study treatment at a reduced dose

#### 4.4.1.11 Hypophosphatemia

Hypophosphatemia has been reported during treatment with cabozantinib. Serum phosphorus should be monitored frequently while receiving cabozantinib. Other causes of hypophosphatemia should be ruled out and/or these causes treated in accordance to standard of care. Mild to moderate hypophosphatemia should be managed by oral replacement including food that are high in phosphate (dairy items, meats, beans) and/or oral phosphate supplements in accordance to standard clinical practice guidelines.

Clinically relevant hypophosphatemia should be managed in accordance to the dose modification guidelines as outlined in Table 4-2 and Table 4-3 or as clinically indicated.

#### 4.4.1.12 Thyroid Function Disorders

Changes in thyroid function tests (TFTs) and hypothyroidism have been reported with cabozantinib therapy and other tyrosine kinase inhibitors as a result of altered thyroid hormone regulation by mechanisms that seem to be specific for each agent.[12] Currently available data are insufficient to determine the mechanism of TFT alterations and its clinical relevance. Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended before initiation and during treatment. Management of thyroid dysfunction (e.g., symptomatic hypothyroidism) should follow accepted clinical practice guidelines and dose modification guidelines as outlined in Table 4-2 and 4-3.

#### 4.4.1.13 Hemorrhagic Events

Hemorrhagic events have been reported with cabozantinib. In order to mitigate risk of severe hemorrhage, subjects should be evaluated for potential bleeding risk factors before initiating treatment and monitored for bleeding events with serial complete blood counts and physical examination while on study. Risk factors for hemorrhagic events may include (but may not be limited to) the following:

- Tumor of the lung with cavitary lesions or tumor lesions which invades, encases, major blood vessels. The anatomic location and characteristics of tumor as well as the medical history must be carefully reviewed in the selection of subjects for treatment;
- Recent or concurrent radiation to the thoracic cavity;
- Active peptic ulcer disease, inflammatory GI diseases including Crohn's disease and ulcerative colitis;
- Underlying medical conditions which affect normal hemostasis (e.g., deficiencies in clotting factors and/or platelet function, or thrombocytopenia);
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis;
- History of clinically significant hemoptysis.

Treatment should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥ 2.5 mL of red blood).

#### 4.4.1.14 GI Perforation/Fistula and Non-GI Fistula Formation

Gastrointestinal perforation/GI fistula: After starting treatment, subjects should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever especially if known risk factors for developing GI perforation or fistula are present.

Discontinue treatment in subjects who have been diagnosed with GI perforation/fistula.

Non-GI fistula formation: Complications from radiation therapy has been identified as a possible predisposing risk factor for fistula formation in subjects undergoing treatment with cabozantinib.

Fistula should be ruled out as appropriate in cases of onset of severe mucositis or difficulty swallowing after start of therapy. Discontinue treatment and initiate appropriate management in subjects who have been diagnosed with a non-GI fistula.

Discontinue treatment in subjects who have been diagnosed with non-GI fistula.

#### 4.4.1.15 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in subjects treated with cabozantinib. Additional risk factors for ONJ have been identified including the use of bisphosphonates and denosumab, chemotherapy, corticosteroids, local radiotherapy, and dental or orofacial surgery procedures.

Caution should be used in subjects receiving bisphosphonates.

Invasive dental procedures should be avoided. In cases where dental procedures are unavoidable, treatment should be held for at least 4 weeks prior to the procedure and resumed after complete wound healing has occurred. Bone healing may often require a protracted time.

#### 4.4.1.16 Respiratory, Thoracic and Mediastinal Disorders

Dyspnea has been reported in clinical studies with cabozantinib and erlotinib. Cough was amongst one of the most common adverse reactions experienced by ≥ 20% of subjects who took erlotinib. Symptoms should be managed according to locally accepted clinical practice including an assessment for underlying causes. Pulmonary embolism should be considered as possible causes for new onset dyspnea given the risk of thrombosis associated with inhibition of VEGF signaling. Furthermore, fistula formation and pneumonia have been reported in subjects treated with cabozantinib and should be considered as clinically indicated in subjects presenting with pulmonary symptoms.

Cases of serious ILD, including fatal cases, can occur with erlotinib treatment. Withhold treatment for acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, and fever pending diagnostic evaluation. If ILD is confirmed, treatment with erlotinib should be permanently discontinued.

#### 4.4.1.17 Renal Failure

Hepatorenal syndrome, severe acute renal failure including fatal cases, and renal insufficiency can occur with erlotinib treatment. Renal failure may arise from exacerbation of underlying baseline hepatic impairment or severe dehydration. Withhold treatment in subjects developing severe renal impairment (CTCAE version 4.03 grade 3 or 4) until renal toxicity is resolved.

#### 4.4.1.18 Ocular Disorders

Decreased tear production, abnormal eyelash growth, keratoconjunctivitis sicca or keratitis can occur with erlotinib treatment and can lead to corneal perforation or ulceration. Discontinue erlotinib if subjects present with corneal perforation or sever ulceration. Withhold erlotinib for keratitis of NCI-CTC version 4.03 grade 3-4 or for grade 2 lasting more than 2 weeks. Withhold and consider discontinuing erlotinib for acute/worsening ocular disorders such as eye pain.

## 4.5 Concomitant Medications and Therapies

### 4.5.1 Anticancer Therapy

Local intervention is discouraged unless medically unavoidable. Subjects receiving local intervention (e.g., palliative radiation) are allowed to continue to receive study treatment at the investigator's discretion.

### 4.5.2 Other Medications

All concomitant medications used by the subject (including prescription and over-the-counter medications, transfusions, vitamins, herbal remedies, and nutritional supplements) during the period from 28 days before the first dose of study treatment through 30 days after the date of the last dose of study treatment are to be recorded in the case report forms.

### 4.5.3 Allowed Therapies

- Antiemetics and antidiarrheal medications are allowed prophylactically in accordance to standard clinical practice if clinically indicated;
- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (e.g., American Society of Clinical Oncology [ASCO] or [European Society for Medical Oncology] ESMO guidelines);
- Drugs used to control bone loss (e.g., bisphosphonates and denosumab) are allowed if started before screening activities but may not be initiated or exchanged during the course of the study and require PI approval;
- Transfusions, hormone replacement, and short term higher doses of corticosteroids should be utilized as indicated by standard clinical practice;
- Individualized anticoagulation therapy with heparin is allowed if it can be provided safely and effectively under the following circumstances:
    - *Low dose heparins for prophylactic use* are allowed if clinically indicated and the benefit outweighs the risk per the investigator's discretion.
    - *Therapeutic doses of low molecular weight heparins (LMWH)* at the time of first dose are allowed if the subject has been on a stable dose of LMWH for at least 6 weeks, and has had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.
    - *Therapeutic doses of low molecular weight heparins (LMWH)* after first dose are allowed if clinically indicated (e.g., for the treatment of deep venous thrombosis), and the benefit outweighs the risk per the investigator's discretion. For

management of thromboembolic complications while on study, refer to Section 4.4.1.8.
    - Accepted clinical guidelines regarding appropriate management while receiving anticoagulation therapy with heparins must be followed. This includes, but is not limited to, subject education regarding potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (e.g., due to kidney dysfunction);
    - For restrictions on oral anticoagulants see Section 4.5.4.
- Administration of the PPI esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers (Study XL184-018). Therefore, concomitant use of gastric pH modifying agents (i.e., PPIs, H2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib. However, co-administration of erlotinib with omeprazole decreased erlotinib AUC by 46%. Please see additional information regarding erlotinib and PPIs (omeprazole and ranitidine in Section 4.5.5). Cimetidine should be avoided with cabozantinib due to potential CYP interactions.

Potential drug interactions are summarized in Section 4.5.5.

### 4.5.4 Prohibited or Restricted Therapies

*The following therapies are <u>prohibited</u> while the subject is on study*:

- Any investigational agent or investigational medical device;
- Therapeutic doses of 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);
- Any other systemic anticancer treatment (e.g., chemotherapy, immunotherapy, radionuclides) and local anticancer treatment such as surgery, ablation, or embolization.

*The following therapies should be <u>avoided</u> if possible, while the subject is on study*:

- Palliative external radiation to bone metastasis for bone pain should not be performed while on study. Subjects who have such an intervention may be considered not evaluable (and may be assigned a censoring or progression date) for certain efficacy endpoints;

- Erythropoietic stimulating agents (e.g., epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence and/or progression associated with erythropoietin;[13]
- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib and erlotinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended;
- Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib or erlotinib because this could significantly increase the exposure to cabozantinib and erlotinib;
- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib and erlotinib concentrations and should be avoided. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib and erlotinib and should be avoided.

Additional information on potential drug interactions with cabozantinib and erlotinib is provided in Section 4.5.5.

### 4.5.5 Potential Drug Interactions

*Cytochrome P450 (CYP):*

Please refer to the drug interaction tables at the following websites for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

Http://medicine.iupui.edu/clinpharm/ddis/table.aspx

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

**Cabozantinib**

Data from a clinical drug interaction study (Study XL184-008) show that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the area under the plasma drug concentration time curve (AUC) of co-administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic,

and by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared with CYP2C8 (i.e., CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate), based on data from in vitro studies. Results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. Strong CYP3A4 inhibitors should be avoided and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended. In addition, cimetidine should be avoided because of its potential to interfere with CYP3A4 mediated metabolism of cabozantinib.

**Erlotinib**

Erlotinib is also metabolized predominately by CYP3A4. Co-treatment with the potent CYP3A4 inhibitor ketoconazole increased erlotinib AUC by 67%. When erlotinib was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2, the erlotinib exposure (AUC)

and maximum concentration increased by 39% and 17% respectively. Dose modifications are recommended and can be made per investigator's discretion in subjects who require strong CYP3A4 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telathromycin, treleandomycin [TAO], voriconazole, grapefruit or grapefruit juice) and CYP3A4 and CYP1A2 inhibitors (e.g., ciprofloxacin). See Table 4-2 for details. Avoid concomitant use if possible. However, subjects taking both cabozantinib and erlotinib, should follow the guidelines for cabozantinib since cabozantinib recommends avoiding CYP3A4 inhibitors.

Pre-treatment by the CYP3A4 inducer rifampicin for 7-11 days prior to erlotinib decreased erlotinib AUC by 58% to 80%. Dose modifications are recommended and can be made per investigator's discretion in subjects who require CYP3A4 inducers (e.g., rifampin, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital, or St. John's Wort). See Table 4-2 for details. Avoid concomitant use if possible. However, subjects taking both cabozantinib and erlotinib, should follow the guidelines for cabozantinib since cabozantinib recommends avoiding CYP3A4 inducers.

*Cigarette smoking:* Cigarette smoking results in reduction in erlotinib AUC. Dose modifications are recommended and can be made per investigator's discretion. See Table 4-2 for details.

*Drugs affecting gastric pH:* Co-administration of erlotinib with omeprazole decreased erlotinib AUC by 46%, and co-administration of erlotinib with ranitidine 300 mg decreased erlotinib AUC by 33%. When erlotinib was administered with ranitidine 150 mg twice daily (at least 10 h after the previous ranitidine evening dose and 2 h before the ranitidine morning dose), erlotinib AUC decreased by 15%. Increasing the dose of erlitinib when co-administered with such agents is not likely to compensate of the loss of exposure. Dose scheduling modifications are recommended in subjects who require ranitidine and antacids (see Section 4.3).

*Protein Binding:* Cabozantinib is highly bound (≥ 99.7%) to human plasma proteins. Therefore, highly protein bound drugs should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect).

*Other Interactions:* Food may increase exposure levels of cabozantinib by 57%, fasting recommendations should be followed. Subjects should fast (with the exception of water) for at least 2 hours after eating the evening meal before taking their dose of cabozantinib. After the 2-

hour fast and before going to bed, subjects are to take cabozantinib with a full glass of water (minimum of 8 oz or 240 mL) with no more food intake for one hour post-dose.

In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-glycoprotein.

Cabozantinib was shown to be a substrate of drug transporter MRP2 in an in vitro assay. Administration of MRP2 inhibitors to subjects may result in increases in cabozantinib plasma concentrations.

Chronic use of modafinil should be avoided because of its potential to reduce cabozantinib exposure (see Investigator's Brochure).

Additional details regarding potential drug interactions with cabozantinib can be found in the Investigator's Brochure.

### 4.6 Compliance

Drug accountability will be assessed with drug dispensing and return records.

### 4.7 Study Drug Accountability

The investigator will maintain accurate records of receipt of all cabozantinib, including dates of receipt. In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused study drug will be reconciled and destroyed in accordance with applicable state and federal regulations.

# 5 STUDY POPULATION

## 5.1 Inclusion Criteria

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

1. The subject has a biopsy-proven diagnosis of adenocarcinoma of the pancreas (or recurrence of previously resected disease) with metastatic disease that is measurable per RECIST 1.1;

2. The subject must have an archived tissue sample such as a prior surgical sample or biopsy sample that is adequate for testing;

3. The subject must have EGFR and c-Met overexpressed in tumor as determined by immunohistochemistry (IHC) test score of 2+ for both markers;

4. The subject has demonstrated radiographic progression after front-line treatment (prior adjuvant therapy allowed if ≥ 6 months elapsed between end of adjuvant therapy and metastatic relapse);

5. The subject is ≥ 18 years old on the day of consent;

6. The subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;

7. The subject has recovery to baseline or ≤ Grade 1 CTCAE v.4.03 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy;

8. The subject has organ and marrow function and laboratory values as follows within 7 days before the first dose of study treatment:

    a. The ANC ≥ 1500/$mm^3$ without colony stimulating factor support;

    b. Platelets ≥ 100,000/$mm^3$;

    c. Hemoglobin ≥ 9 g/dL;

    d. Bilirubin ≤ 1.5 × the ULN. For subjects with known Gilbert's disease, bilirubin ≤ 3.0 mg/dL;

e. AST/ALT ≤ 3 x the ULN;

f. Serum albumin ≥ 2.8 g/dl;

g. Serum creatinine ≤ 1.5 × the ULN or creatinine clearance (CrCl) ≥ 40 mL/min. For creatinine clearance estimation, the Cockcroft and Gault equation should be used:

i. Male: CrCl (mL/min) = (140 - age) × wt (kg) / (serum creatinine × 72);

ii. Female: Multiply above result by 0.85;

h. UPCR ≤ 1;

i. Serum phosphorus, calcium, magnesium and potassium ≥ LLN;

j. Prothrombin time (PT)/INR or partial thromboplastin time (PTT) test < 1.3 × the ULN *within 7 days* before the first dose of study treatment;

9. The subject is capable of understanding and complying with the protocol requirements and has signed the informed consent document;

10. The subject has a life expectancy of 12 weeks or greater;

11. The subject is able to tolerate oral medications and no evidence of ongoing malabsorption;

12. All sexually active subjects of reproductive potential must agree to use both a medically accepted barrier method (e.g., male or female condom) and a second method of birth control during the course of the study and for 4 months after the last dose of study drug(s);

13. Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (i.e., females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy or bilateral oophorectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons.

## 5.2 Exclusion Criteria

A subject who meets any of the following criteria is ineligible for the study:

1. The subject has received cytotoxic chemotherapy or biologic agents (e.g., cytokines or antibodies) within 14 days, or nitrosoureas/mitomycin C within 6 weeks before the first dose of study treatment;

2. Prior treatment with cabozantinib or erlotinib;

3. Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before the first dose of study treatment. Systemic treatment with radionuclides within 6 weeks before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible;

4. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 14 days before the first dose of study treatment;

5. The subject has received any other type of investigational agent within 28 days before the first dose of study treatment;

6. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before the first dose of study treatment. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of the start of study treatment;

7. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (e.g., warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (e.g., clopidogrel);

   Note: Low-dose aspirin for cardioprotection (per local applicable guidelines) and low-dose LMWH are permitted. Anticoagulation with therapeutic doses of LMWH is allowed in subjects who are on a stable dose of LMWH for at least 6 weeks before first dose of study treatment, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.

8. The subject has experienced any of the following:

a. clinically-significant GI bleeding within 6 months before the first dose of study treatment;

b. hemoptysis of ≥ 0.5 teaspoon (2.5ml) of red blood within 3 months before the first dose of study treatment;

c. any other signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment; and

d. clinically confirmed history of interstitial lung disease (ILD).

9. The subject has radiographic evidence of cavitating pulmonary lesion(s);

10. The subject has tumor invading a major blood vessel (encasement of local vascular structures is not exclusionary).

11. The subject has evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of cabozantinib which in the opinion of the investigator places the subject at greater risk of perforation.

12. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

    a. Cardiovascular disorders including:

        i. Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening;

        ii. Concurrent uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment;

        iii. Any history of congenital long QT syndrome;

        iv. Any of the following within 6 months before the first dose of study treatment:

- unstable angina pectoris;
- clinically-significant cardiac arrhythmias;
- stroke (including transient ischemic attack (TIA), or other ischemic event);
- myocardial infarction.

b. GI disorders particularly those associated with a high risk of perforation or fistula formation including:

i. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (e.g., Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction

ii. Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before first dose of study treatment

Note: Complete healing of an intra-abdominal abscess must be confirmed prior first dose of study treatment

c. Other clinically significant disorders that would preclude safe study participation;

13. Major surgery within 12 weeks before the first dose of study treatment. Complete wound healing from major surgery must have occurred 1 month before the first dose of study treatment. Minor surgery (including uncomplicated tooth extractions) within 28 days before the first dose of study treatment with complete wound healing at least 10 days before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior surgery are not eligible;

14. QTcF > 500 msec within 1 month before the first dose of study treatment:

a. Three ECGs must be performed for eligibility determination. If the average of these three consecutive results for QTcF is ≤ 500 msec, the subject meets eligibility in this regard.

15. Pregnant or lactating females;

16. Active smoker;

17. Inability to swallow intact tablets;

18. Previously identified allergy or hypersensitivity to components of the study treatment formulations;

19. Diagnosis of another malignancy within 2 years before the first dose of study treatment, except for superficial skin cancers, or localized, low grade tumors deemed cured and not treated with systemic therapy; malignancy felt by investigator to potentially affect subject survival or ability to evaluate disease response.

# 6 STUDY ASSESSMENTS AND PROCEDURES

The following schedule of assessments applies to all subjects (see Section 6.1). More frequent assessments should be obtained if clinically indicated.

## 6.1 Schedule of Assessments

| | **Pre-Treatment Period** | | **Study Treatment Period** (cycles done every 28 ± 5 days) | | | | | **Post-Treatment Period** | **Survival Follow-Up** |
|---|---|---|---|---|---|---|---|---|---|
| | Within 28 days before 1st Dose of Study Treatment | Within 7 days before 1st dose of Study Treatment | Cycle 1/Day 1 | Cycle 1D15 | C2D1 | C2D15 | C3D1 and beyond will be done every 4 weeks (± 5 days) | 30 - 37 Days after last dose | Every 3 months for up to 2 years after treatment discontinuation |
| Administrative Procedures | | | | | | | | | |
| Informed consent | X | | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | | |
| Demographics | X | | | | | | | | |
| Medical and cancer history | X | | | | | | | | |
| Registration | X | | | | | | | | |
| Prior and concomitant medication review | X | X | X | X | X | X | X | X | |
| Safety follow-up | | | | | | | | X | |
| Survival follow-up | | | | | | | | | X[1] |
| Clinical Procedures/Assessments | | | | | | | | | |
| Adverse events/patient drug compliance | X[2] | | X | X | X | X | X | X[3] | |
| Physical examination[4] | X | | X | X | X | X | X | X | |
| Vital signs[5] | | X | X | X | X | X | X | X | |
| ECOG performance status | X | | X | X | X | X | X | X | |
| 12-lead ECG | X | X | | | X | | X | | |

| | **Pre-Treatment Period** | | **Study Treatment Period** (cycles done every 28 ± 5 days) | | | | | **Post-Treatment Period** | **Survival Follow-Up** |
|---|---|---|---|---|---|---|---|---|---|
| | Within 28 days before 1st Dose of Study Treatment | Within 7 days before 1st dose of Study Treatment | Cycle 1/Day 1 | Cycle 1D15 | C2D1 | C2D15 | C3D1 and beyond will be done every 4 weeks (± 5 days) | 30 - 37 Days after last dose | Every 3 months for up to 2 years after treatment discontinuation |
| Laboratory Assessments | | | | | | | | | |
| Complete blood count with differential | | X | | X | X | X | X | X | |
| Comprehensive serum chemistry panel | | X | | X | X | X | X | X | |
| Urinalysis with UPCP | | X | | X | X | X | X | X | |
| PT/INR, PTT | | X | | X | X | X | X | | |
| TSH, free T3, free T4 | | X | | X | X | X | X | | |
| CA19-9 | | X[11] | | | X | | X | | |
| Pregnancy test (urine or serum)[9] | | X | | | X | | X | X | |
| Treatment | | | | | | | | | |
| Cabozantinib and erlotinib administration | | | X (daily) | | | | | | |
| Disease Assessment | | | | | | | | | |
| Contrast enhanced CT or MRI[6] | X | | | | | | X (every 8 weeks) | | |
| Archival Tissue Collection/Correlative Studies | | | | | | | | | |
| Blood sample collection[8] | | | X[10] | X | X | | X | | |
| Tissue sample collection[8] | X[7] | | | | | | | | |

**Footnotes:**

1. Follow-up may be done by medical record review or phone call to subject and/or next of kin.

2. Subjects will be monitored for adverse events (AEs) from the time of first study intervention (i.e., biopsy, if needed, or treatment, whichever comes first).

3. Additional follow-up will occur for subjects with AEs related to study treatment that are ongoing at the time of this visit, and for subjects with SAEs related to study treatment that occur after the time of this visit.

4. A Full physical exam will be done in the pre-treatment period and on Cycle 1/Day 1. Physical exams may also be done by the investigator or qualified designee throughout participation in the trial as clinically indicated.

5. Vital signs include: height (at screening only), weight, temperature, pulse, respiratory rate, and blood pressure.

6. All sites of known disease must be assessed.

7. Patients will be asked for archival tissue during the screening period. Archival tissue is required pre-treatment as part of study eligibility to test for EGFR and c-MET expression. KRAS will also be tested if previous KRAS testing was not done or results are unknown AND there is adequate tissue available from tissue collected at screening

8. Only samples collected from eligible patients during the screening period will be utilized for the correlative studies which are outlined in this trial. Samples collected from ineligible patients during screening will be discarded.

9. Only for women of childbearing potential.

10. This sample may be collected any time after enrollment so long as it occurs before the patient takes his/her first dose of study medication on Cycle 1/Day 1.

11. The window for this test is within 28 days of starting treatment.

## 6.2 Pre-Treatment Period

During the Pre-Treatment Period, subjects are consented and qualified (screened) for the study. Informed consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this study. There is a separate screening consent for this trial. Evaluations performed as part of routine care before informed consent can be considered as screening evaluations if done within the defined screening period.

Study eligibility is based on meeting all of the study inclusion criteria and none of the exclusion criteria at screening and on Study Day 1 before study treatment administration. For each subject, the Pre-Treatment Period ends upon receipt of the first dose of study treatment or final determination that the subject is ineligible for the study.

The following assessments will be conducted before subjects receive their first dose of cabozantinib and erlotinib on this protocol:

### 6.2.1 Administrative Procedures

#### 6.2.1.1 Recruitment and Registration

Applicable regulatory documents must be completed and on file prior to registration of any subjects. Potential patients will be identified in the Oncology outpatient clinics or by referrals from outside physicians. Patients who appear to be eligible for this trial will undergo the Informed Consent Process and be screened for eligibility utilizing the Eligibility Criteria.

#### 6.2.1.2 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB's approval in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to

continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature if the new information would affect the subject's willingness to continue participation in the study as determined by the IRB.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor requirements.

#### 6.2.1.3 Inclusion/Exclusion Criteria

The completed Eligibility Checklist will be forwarded to the Indiana University Simon Cancer Center (IUSCC) Clinical Trials Office (CTO) designee for eligibility verification.

#### 6.2.1.4 Medical and Cancer History

A medical history will be obtained by the investigator or qualified designee during the screening period. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

The investigator or qualified designee will obtain prior and current details regarding cancer disease status and will review all prior cancer treatments including systemic treatments, radiation, and surgeries.

#### 6.2.1.5 Registration

The original signed IRB approved Informed Consent Document and completed Eligibility Checklist will be forwarded to the IUSCC CTO designee for eligibility verification and registration in the OnCore® database. Notification will be sent to the Principal Investigator (PI), treating physician and research nurse when registration is complete to confirm registration and inform them of the subject ID number.

#### 6.2.1.6 Prior and Concomitant Medications Review

During the screening period, the investigator or qualified designee will review prior medication use (including prescription and over-the-counter medications, transfusions, vitamins, herbal

remedies, and nutritional supplements and any protocol-specified washout requirement) and record prior medication taken by the subject within 28 days before written informed consent. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs should be recorded as defined in Section 7.1.4.

## 6.3 Treatment Period

During the Treatment Period subjects will receive cabozantinib and erlotinib until either disease progression, the occurrence of unacceptable drug-related toxicity or for other reason(s) for subject withdrawal as described in Section 3.6.

If the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (e.g., clinic closure, personal emergency, inclement weather, vacation), the assessment should be performed as close as possible to the required schedule.

Regular tumor assessments should be performed in accordance to the guidelines in Section 6.3.1.8 to determine if PD is present.

The Treatment Period ends when a subject receives his or her last dose of study treatment; the subject then enters the Post-Treatment Period.

### 6.3.1 Clinical Procedures

#### 6.3.1.1 Adverse Event Monitoring

Subjects should be instructed to immediately inform the PI of any AEs. Subjects experiencing dizziness, sleepiness, or other symptoms that could influence alertness or coordination should be advised not to drive or operate other heavy machinery.

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Schedule of Assessments and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.03. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to Section 7.1 for detailed information regarding the assessment and recording of AEs.

#### 6.3.1.2 Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period and on Cycle 1/Day 1. Clinically significant abnormal findings should be recorded as medical history. Physical exams may also be done by the investigator or qualified designee throughout participation in the trial as clinically indicated.

#### 6.3.1.3 Vital Signs

The investigator or qualified designee will take vital signs at screening and per the Schedule of Study Assessments in Section 6.1. Vital signs should include: height at screening only, weight, temperature, pulse, respiratory rate, and blood pressure.

#### 6.3.1.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at screening and per the Schedule of Study Assessments in Section 6.1.

#### 6.3.1.5 Electrocardiogram (ECG)

The investigator or qualified designee will perform a 12-lead ECG at screening and every 4 weeks beginning Cycle 2/Day 1. Up to 2 ECGs may be done during screening as one must be within 7 days of starting treatment.

#### 6.3.1.6 Laboratory Assessments

Abnormalities in clinical laboratory tests that lead to a change in subject management (e.g., dose delayed [withheld] or reduced, requirement for additional medication, treatment or monitoring) are considered clinically significant for the purposes of this study, and will be recorded on the Adverse Events Case Report Form (CRF). If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE.

| **Laboratory Assessments** | | |
|---|---|---|
| **Hematology**<br>• WBC count with differential (including at minimum: neutrophils, basophils, eosinophils, lymphocytes, monocytes) | • hematocrit<br>• platelet count<br>• RBC count<br>• hemoglobin | |
| **Serum chemistry**<br>• albumin<br>• ALP<br>• amylase<br>• ALT<br>• AST<br>• bicarbonate<br>• BUN<br>• chloride | • creatinine<br>• GGT<br>• glucose<br>• ionized calcium or total and corrected calcium<br>• lactate dehydrogenase<br>• lipase | • magnesium<br>• phosphorus<br>• potassium<br>• sodium<br>• total bilirubin<br>• total protein |
| **Urinalysis**<br>• appearance<br>• color<br>• pH<br>• specific gravity<br>• ketones<br>• protein<br>• UPCR | • glucose<br>• bilirubin<br>• nitrite<br>• creatinine<br>• urobilinogen | • occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive) |
| **Other**<br>• TSH, Free T3 and T4<br>• Pregnancy test (urine or serum) for women of child-bearing potential | • PT/INR, PTT<br>• CA19-9 | |

#### 6.3.1.7 Subject Drug Compliance

Subjects will be asked about drug compliance and any adverse events he or she may experience during clinic visits. Any discrepancies in drug accountability will be clarified with the subject.

#### 6.3.1.8 Disease Assessment

Contrast enhanced imaging studies (CT or MRI) will be performed at screening and every 8 weeks beginning Cycle 3/Day 1. All sites of known disease must be assessed. CT modalities should be done according to standard of care for the subject's disease.

### 6.4 Post-Treatment Period

#### 6.4.1.1 Safety Follow-Up

Subjects will return to the study site 30 to 37 days after their last dose of study drugs to complete end-of-study safety assessments.

Laboratory and physical examinations will be performed. Remaining study treatment will be returned by the subject, and treatment compliance via subject drug diaries will be documented. Additional follow-up will occur for subjects with AEs related to study treatment that are ongoing at the time of this visit, and for subjects with SAEs related to study treatment that occur after the time of this visit.

### 6.5 Survival Follow-Up

Subjects will be followed every 3 months for up to 2 years after treatment discontinuation for survival via medical record review or phone call to the subject and/or next of kin.

### 6.6 Correlative Studies

HGF and its receptor, c-Met (also known as Met and MET), are also overexpressed in PDAC. c-Met also heterodimerizes with EGFR, and EGFR-Met cross-talk may contribute to chemoresistance. Np-1 and Np-2, which are transmembrane proteins that act as co-receptors for VEGF-A, HGF, and class 3–secreted semaphorins, are also overexpressed in PDAC, and Np-1 associates with Met, enhancing HGF's ability to promote migration and invasion in pancreatic cancer cells (PCCs), as previously reported by us. Np-1, which does not associate with EGFR, can signal via integrin beta 1 (ITG-β1) to promote PCC invasion and survival. ITG-β1, which is also overexpressed in PDAC, can enhance EGFR signaling. Together, these observations point to a previously unrecognized signaling node in PDAC that consists of Met/EGFR/Np-1/2, and ITG-β1. In this proposal, we will test the hypothesis that it is possible to target this signaling node by dual inhibition of Met with cabozantinib and EGFR with erlotinib.

Based on the above, we will analyze tumor tissue to assess expression of c-Met and EGFR by RT-qPCR and immunohistochemistry. Immunostaining will be conducted by Indiana University Health Department of Pathology on baseline samples and in the Korc laboratory for samples collected post-treatment using the same standard operating procedures (SOPs). SOPs will include same antibodies and antibody titers, and same antigen exposure procedures. The advantages of using the RT-qPCR and immunohistochemistry approaches is that they are easy to execute rapidly and may yield important information for trial design and interpretation. By rapidly performing RT-qPCR for HGF, c-Met, and EGFR, we will be able to accurately evaluate which PDAC samples express high levels of all three transcripts, and consider these patients as candidate for the clinical trial, even before performing the more sophisticated studies on the tumors as outlined above. In addition, we will assess expression of Np-1, ITG-b1, p-EGFR and p-c-Met by immunostaining and/or immunofluorescence.

We will perform contrast enhanced CT or MRI every 8 weeks with additional correlative studies on blood and tissue collected at baseline (pre-treatment) and Cycle 1/Day 15 (post-treatment) to measure Met and EGFR mRNA by qPCR, blood collection to assay plasma HGF and soluble Met receptor, and to evaluate Met and EGFR total phosphoprotein levels by electro-luminescent 2-site immunoassays in tissue to determine if these assays can serve as predictors of response to therapy.

All patients must have archival tissue for EGFR and c-Met expression testing by immunohistochemistry (IHC) as only patients with a test score of 2+ for both markers will be eligible to participate in this trial. Patients will be asked for archival tissue during the screening period (i.e. at baseline). It is anticipated that most patients who may be eligible for this study will have archival tissue available for screening. Patients without archival tissue are ineligible. Tumor tissue is required pre-treatment as part of study eligibility criteria to test for EGFR and c-MET expression. KRAS will also be tested if previous KRAS testing was not done or results are unknown AND there is adequate tissue available from tissue collected at screening. Archival tissue obtained may come from previous EUS or CT-guided biopsies or surgical resection. FNA cores are acceptable. Primary lesion tissue (typically obtained via EUS-guided biopsy or surgical resection) is preferred; however, metastatic lesion tissue may also be used (typically obtained via CT-guided biopsy). Only samples collected from eligible patients during the screening period will be utilized for the correlative studies which are outlined in this trial. Tissue samples collected from ineligible patients during screening will be discarded.

Approximately 20 ml of blood will be collected at baseline (during screening period or prior to first administration of study drug on Cycle 1/Day 1) and beginning Cycle 1/Day 15 and every 4 weeks thereafter (i.e. Cycle 2/Day 1, Cycle 3/Day 1, Cycle 4/Day 1, etc.). Only samples collected from eligible patients during the screening period will be utilized for the correlative studies which are outlined in this trial. Blood samples collected from ineligible patients during screening will be discarded.

Complete details regarding tissue and blood collection, processing, transfer and storage information for these correlative studies can be found in the Laboratory Manual for this study.

# 7 SAFETY

## 7.1 Definitions of Adverse Events

### 7.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject who has been enrolled in a clinical study and who may have been given an investigational product, regardless of whether or not the event is assessed as related to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, regardless of whether or not the event is assessed as related to the investigational product. Pre-existing medical conditions that worsen during a study should be recorded as AEs. Abnormal laboratory values, ECG findings, or vital signs are to be recorded as AEs if they meet the criteria described in Section 4.3 and 4.4.

All untoward events that occur after patient begins study treatment through 30 after the decision to discontinue study treatment (or the date the subject is deemed to be a screen failure) are to be recorded by the investigational site. This requirement includes AEs from unscheduled as well as scheduled visits.

### 7.1.2 Suspected Adverse Reactions (SAR)

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

Examples of types of evidence that would suggest a causal relationship between the drug and the adverse event:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome).
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

### 7.1.3 Adverse Reaction (AR)

An adverse reaction is any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

### 7.1.4 Serious Adverse Events

The SAE definition and reporting requirements are in accordance with the International Conference of Harmonisation (ICH) Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Topic E2A.

An SAE is defined as any untoward medical occurrence that at any dose:

- Result in death;
- Is immediately life-threatening (i.e., in the opinion of the investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death);
- Requires inpatient hospitalization ≥ 24 hours or prolongation of existing hospitalization
    - NOTE: Hospitalizations that are not considered SAEs are:
        - Hospitalization planned prior to first administration of study drug
        - Hospitalization for less than 24 hours
        - Hospitalization for elective treatment of a pre-existing condition unrelated to the study medication
- Results in persistent or significant disability or incapacity:

- Note: The term “disability” refers to events that result in a substantial disruption of a subject’s ability to conduct normal life function.

- Is a congenital anomaly or birth defect;
- Is an important medical event (IME):
  - Note: The term “important medical event” refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed under the definition of SAE. Examples of IMEs include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of product dependency or product abuse.
- Pregnancy
  - Pregnancy of a female subject during the study or within 30 days after the last dose of study drug should be reported via an SAE report. Additional details regarding pregnancy can be found in Section 6.3.3.

### 7.1.5 Unexpected Adverse Events

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the Reference Safety Information section (Appendix K) of the Investigator’s Brochure (cabozantinib), Adverse Reactions section of the Package Insert (erlotinib), or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

This definition relies entirely on the adverse events or suspected adverse reactions listed in the investigator brochure for the particular drug under investigation (or elsewhere in the general investigational plan if an investigator brochure is not required or available) as the basis for determining whether newly acquired information generated from clinical trials or reported from other sources is unexpected. This means that events not listed for the particular drug under

investigation in the investigator brochure are considered "unexpected" and those listed are considered "expected." When new adverse event information is received, it is the PI's responsibility to determine whether the event is "unexpected" for IND safety reporting purposes. In the clinical trial setting, there has been some confusion with the term "expected" as it has been used to mean "anticipated" for the disease being treated or population being studied rather than "listed in the investigator brochure." For example, some adverse events can be anticipated to occur as a result of a disease or in an older population (e.g., cancer-related deaths in a cancer trial, strokes or acute myocardial infarctions in an older population). However, for reporting purposes, these anticipated events are not "expected" because they are not listed in the investigator brochure (i.e., the test drug is not suspected or known to cause them).

Adverse events listed in the investigator brochure as occurring with members of the same class of drugs, or as anticipated from the pharmacological properties of the drug, would be considered unexpected until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the angiotensin-converting enzyme (ACE) inhibitor class and angioedema would be described in the investigator brochure as a class effect, a case of angioedema observed with the drug under investigation should be considered unexpected for reporting purposes until it is included in the investigator brochure as occurring with the drug under investigation.

### 7.1.6 Determining Attribution to the Investigational Agents

An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily *"caused by a therapeutic intervention"*. After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

| Relationship | Attribution | Description |
|---|---|---|
| Unrelated to investigational agent/intervention | Unrelated | The AE is clearly **NO**T related |
| | Unlikely | The AE is **doubtfully related** |
| Related to investigational agent/intervention | Possible | The AE **may be related** |
| | Probable | The AE **is likely related** |
| | Definite | The AE **is clearly related** |

## 7.2 Adverse Event Reporting Requirements

### 7.2.1 Reporting to the IRB

1. Unanticipated problems involving risks to subjects or others will be reported promptly to the IRB if they:

- unexpected;
- related or possibly related to participation in the research; and
- suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the adverse event does not meet all three (3) criteria listed above, the event does not have to be promptly reported to the Indiana University IRB. However, it should be reported at the time of continuing review.

2. Prompt reporting of unanticipated problems to the IRB is defined as within 5 days from becoming aware of the event.

### 7.2.2 Reporting to Exelixis

#### 7.2.2.1 SAEs

As soon as an investigator becomes aware of an AE that meets the definition of 'serious,' this should be documented to the extent that information is available.

- IUSCC shall notify Exelixis within twenty-four (24) hours of making such discovery by submitting a completed SAE report form and any other pertinent SAE information as indicated on the SAE reporting form;
- The SAE reporting form must be submitted to Exelixis even if it is not felt to be drug related;
- Pregnancy (for a subject or for the partner of a subject), although not itself an SAE, should also be reported on a pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities;
- SAEs that must be recorded on an SAE Reporting form include the following:
    - all SAEs that occur after informed consent and through 30 days after the decision to discontinue study treatment (or the date the subject is deemed to be a screen failure);
    - any SAEs assessed as related to study treatment or study procedures, even if the SAE occurs more than 30 days after the decision to discontinue study treatment;

- although most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows: elective or previously scheduled surgeries or procedures for pre-existing conditions that have not worsened after initiation of treatment (e.g., a previously scheduled ventral hernia repair); pre-specified study hospitalizations for observation; or events that result in hospital stays of fewer than 24 hours and that do not require admission (e.g., an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics). SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

IUSCC will report to Exelixis all SAEs that are sent to the FDA at the time of submission to the FDA. Follow-up information will be provided to Exelixis as reasonably requested. Send SAE reports on the MedWatch Report Form to:

**Exelixis Drug Safety**
**Facsimile:** (650) 837-7392
**Email:** drugsafety@exelixis.com

#### 7.2.2.2 Study Initiation

IUSCC will provide the following to Exelixis prior to initiation of Exelixis support (provision of product and/or funding):

- Final study protocol
- Fully executed IST Agreement
- Regulatory Response Documentation (IND or CTA documentation if applicable)
- IRB/IEC approval

#### 7.2.2.3 Study Maintenance

Throughout the study, IUSCC will provide the following to Exelixis:

- At least one safety study status update per year, to include information on enrollment and study completion dates.
- *Immediate* notification of any amendments made due to safety reasons.

#### 7.2.2.4 Study Closure

IUSCC will provide Exelixis a copy of the IND Annual Report. Upon study closure, IUSCC will certify that all safety reporting obligations were met.

### 7.2.3 Reporting to the FDA

Per CFR 312.32 (c), the investigator-sponsor of the IND must notify the Food and Drug Administration (FDA) and all participating investigators in a written IND safety report of any adverse experience. There are two types of reports to the FDA: 7-day and 15-day reports.

#### 7.2.3.1 15-Day IND Reports:

The investigator-sponsor of the IND must notify the Food and Drug Administration (FDA) and all participating investigators in a written IND safety report of any:

- **suspected adverse reaction that is *both***
- **serious *and***
- **unexpected**

Each written notification shall be made as soon as possible, and no later than **15 calendar** days after the investigator-sponsor's initial receipt of the information.

#### 7.2.3.2 7-Day Reports:

The investigator-sponsor must notify FDA and all participating investigators in a written IND safety report of any adverse experience:

- **fatal or life-threatening experience that is *both***
- **associated with use of the drug *and***
- **unexpected**

The FDA will be notified as soon as possible but no later than **7 calendar** days after initial receipt of the information.

#### 7.2.3.3 Report Content:

Each written notification may be submitted on FDA Form 3500A or in a narrative format and must bear prominent identification of its contents, i.e., "IND Safety Report". For purposes of this protocol, the **MedWatch Report Form (FDA 3500A mandatory reporting), along with FDA Form 1571, and a cover letter** submitted to the appropriate FDA division, will serve as the written IND safety report. Follow-up information to a safety report should be submitted as soon as the relevant information is available.

Submit:

- MedWatch Report Form (FDA 3500A)

- FDA Form 1571
- Cover Letter

The IUSCC Protocol Development Coordinator should be contacted to assist with all FDA submissions and will be provided with a copy of all events that are reported to the FDA. All IND submissions will be maintained in a master file in the Clinical Trials Office of the IU Simon Cancer Center.

### 7.2.4 Reporting to Participating Sites

Exelixis will send IND safety reports from external studies that involve the study drug to the Multicenter Network Associate Administrator, or designee. The Multicenter Network Associate Administrator, or designee, will forward the safety reports to the sponsor-investigator, or designee, who will review these reports and determine if revisions are needed to the protocol or consent. IUSCC will forward these reports to participating sites every 2 weeks.

For IND safety reports originating from this study, IUSCC will distribute reports which are serious, unexpected and associated with the study intervention (possibly, probably or definitely related) to all participating sites in the form of an Expedited Safety Report (external safety/IND safety report) within 15 calendar days from determination that the suspected adverse reaction qualifies for reporting. Copies of these External Safety Reports will be kept on file in the IUSCC CTO. Upon receipt from IUSCC, site investigators, or designees, are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

Exelixis reserves the right to upgrade the investigator assessment of an SAE based on sponsor-investigator reporting responsibilities.

## 7.3 Other Safety Considerations

### 7.3.1 Laboratory Data

All laboratory data required by this protocol and any other clinical investigations should be reviewed. Any abnormal value that leads to a change in subject management (e.g., dose reduction or delay or requirement for additional medication or monitoring) or that is considered to be of clinical significance by the investigator should be reported as an AE or SAE as appropriate.

### 7.3.2 Pregnancy

If a subject becomes pregnant during the study, she will be taken off study treatment and will be followed through the end of her pregnancy. The investigator must inform the PI of the

pregnancy. Forms for reporting pregnancies 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 or designee. 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.

### 7.3.3 Medication Errors/Overdose

Any study drug administration error or overdose that results in an AE, even if it does not meet the definition of serious, requires reporting within 24 hours to Exelixis or designee.

### 7.3.4 Follow-Up of Adverse Events

Any related SAEs or any AEs assessed as related that led to treatment discontinuation, including clinically significant abnormal laboratory values that meet these criteria, ongoing 30 days after the decision to discontinue study treatment must be followed until either resolution of the event or determination by the investigator that the event has become stable or irreversible. This follow-up guidance also applies to related SAEs that occur ***> 30 days after the decision to discontinue*** study treatment. The status of all other continuing AEs will be documented as of 30 days after the decision to discontinue study treatment.

## 8 STATISTICAL CONSIDERATIONS

### 8.1 General Considerations

Statistical analysis of this study will be the responsibility of the Department of Biostatistics at Indiana University School of Medicine. Parameter estimates and relevant summary statistics will be reported for both efficacy and safety outcomes. Continuous variables will be summarized by means, medians, minima, maxima and standard deviations. Categorical variables will be summarized by frequencies and percentages. Missing data will not be imputed. Additional exploratory analysis will be conducted when appropriate. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol. The statistical analysis methods are outline below.

### 8.2 Study Design

This is a single arm two-stage Phase II study. No randomization or blinding is involved.

### 8.3 Definition of Endpoints

Objective response (radiographic response) rate: proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence

(taking as reference for progressive disease the smallest measurements recorded since the start of treatment)

Disease control rate: proportion of all subjects with stable disease (SD) for 8 weeks, or partial response (PR), or complete response (CR) according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

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

Overall survival (OS): a measurement from the date of first treatment until death from any cause.

Safety: Adverse event terms recorded in the eCRFs defined by the National Cancer Institute (NCI) CTCAE v4.03. Seriousness, severity grade and relationship to study treatment will be assessed by the investigator.

## 8.4 Analysis Population

### 8.4.1 Enrolled Population

The enrolled population comprises all patients who meet the eligibility criteria and are registered onto the study.

### 8.4.2 Safety Population

The safety population comprises all patients who have received at least one dose of the study medication. This set will be used for safety analysis.

### 8.4.3 Efficacy Population

The efficacy population comprises all patients who have received at least one dose of the study medication, have been evaluated for the primary endpoint, and have no significant protocol violations. This population will be used for efficacy analysis.

## 8.5 Sample Size, Accrual and Study Duration

The optimal two-stage design to test the null hypothesis that $P \leq 0.025$ versus the alternative that $P \geq 0.150$ has an expected sample size of 17.32 and a probability of early termination of 0.757. If the drug is actually not effective, there is a 0.045 probability of concluding that it is (the target for this value was 0.050). If the drug is actually effective, there is a 0.198 probability of

concluding that it is not (the target for this value was 0.200). After testing the drug on 11 patients in the first stage, the trial will be terminated if 0 respond. If the trial goes on to the second stage, a total of 37 patients will be studied. If the total number responding is less than or equal to 2, the combination is rejected. To allow for a few patients being not evaluable for efficacy, up to 40 subjects may be enrolled. It is estimated that two patients per month will meet eligibility criteria. As such we estimate 6 months to complete the first cohort and 15 months to complete enrollment to the second cohort. Average follow-up is expected to be 9 months to a year.

### 8.6 Patient Characteristics

Baseline patient characteristics will be tabulated in the enrolled population, such as demographics (age, race, gender), and disease characteristics (tumor location, stage).

### 8.7 Significant Protocol Violations

Significant protocol violations such as with respect to eligibility criteria and treatment plan will be tabulated.

### 8.8 Safety Analysis

The safety population will be used for all safety analysis. All safety data will be listed. For the treatment-emergent AEs, namely AEs started or worsened during the on-treatment period, the incidence will be summarized by system organ class and/or preferred term, severity based on CTCAE grades, type of adverse event and the relation to the study drug. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

### 8.9 Efficacy Analysis

An exact binomial test will be used to test the hypothesis that radiographic response (ORR) is greater than 15%). ORR and DCR will be estimated with 95% exact binomial confidence intervals. Median PFS and OS will be estimated using 95% confidence intervals based on the exponential distribution. Safety and tolerability data will be tabulated.

### 8.10 Correlative Analysis

c-Met and EGFR levels as quantitated by RT-qPCR will be compared to c-Met and EGFR biomarkers as determined by IHC using Bland-Altman plots and intra-class correlation measures. All biomarkers, both pre-treatment and changes over time will be correlated with PFS using Cox proportional hazards regression. Time dependent ROC curves will be generated to assess predictive ability.

### 8.11 Interim Analysis/Criteria for Stopping Study

After testing the drug on 11 patients in the first stage, the trial will be terminated if 0 respond. If the trial goes on to the second stage, a total of 37 patients will be studied. If the total number responding is less than or equal to 2, the combination is rejected.

## 9 DATA AND SAFETY MONITORING

This study will be conducted in accordance with the IU Simon Cancer Center Institutional DSMP for **High Risk Trials.** Investigators will conduct continuous review of data and subject safety. Weekly review meetings for high risk trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). Weekly meeting summaries should include review of data and subject safety by including for each dose level: the number of subjects, significant toxicities as described in the protocol, dose adjustments and responses observed. Study teams should maintain meeting minutes and attendance for submission to the DSMC upon request.

### 9.1 Data and Safety Monitoring Committee

The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study semi-annually to review overall trial progress, toxicity, compliance, data integrity, and accrual per the Institutional DSMP.

Furthermore, the DSMC conducts an administrative review of serious adverse events (SAEs), deviations, reportable events, and any other outstanding business. Major issues may require further DSMC review or action.

For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure or package insert), the principal investigator will notify the DSMC Chair immediately. The notification will include the incidence of study adverse events, grades, and attributions, as well as investigator statements regarding comparison with risks per the IB/ package insert.

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the subject warrant early closure of the study, the DSMC Chair and Compliance Officer must be notified within 1 business day via email, and the IRB must be notified within 5 business days. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review

## 9.2 IND Annual Reports

For trials with an IND held locally by the IU principal investigator or university, the IND Annual Report will be reviewed by the DSMC.

## 9.3 Study Auditing and Monitoring

All trials conducted at the IUSCC are subject to auditing and/or monitoring per the Institutional DSMP. Reports will be reviewed by the full DSMC at the time of study review.

## 9.4 Oncore Reporting Requirements

The DSMC reviews data and study progress directly from Oncore; therefore, timely data entry and status updates are vital. Study data must be entered within Oncore promptly, no later than one week from study visit occurrence. Subject status in Oncore will be updated in real time, as this may affect overall trial enrollment status. Global SAEs and deviations will be reviewed on a monthly basis by the DSMC Chair directly from Oncore.

## 9.5 Study Accrual Oversight

Accrual data will be entered into the IU Simon Cancer Center OnCore system. The Protocol Progress Committee (PPC) reviews study accrual twice per year, while the PPC coordinator reviews accrual quarterly.

## 9.6 Oncore Safety Reporting

In addition to protocol- and regulatory-required safety reporting, all serious adverse events (SAEs) will be captured in the Oncore system within 1 business day of notification. Initial SAE reporting will include as much detail as available, with follow-up to provide complete information.

Attributions will be assessed to study drugs, procedures, study disease, and other alternate etiology.

## 9.7 Protocol Deviation Reporting

Protocol deviations will be entered into OnCore within 5 days of discovery and reviewed by the DSMC Chair on a monthly basis. Findings will be reported to the full DSMC at the time of study review. For serious or repetitive protocol deviations, additional action may be required by the DSMC.

# 10 ETHICAL ASPECTS

## 10.1 Local Regulations

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" (GCP) ICH E6 Tripartite Guideline (January 1997). The investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 Code of Federal Regulations, subpart D, Part 312, "Responsibilities of Sponsors and Investigators" Part 50, "Protection of Human Subjects" and Part 56, "Institutional Review Boards."

## 10.2 Informed Consent

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

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

The CRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All subjects (including those already being treated) should be informed of the new information, should be given a copy of the revised form, and should give their consent to continue in the study.

## 10.3 Institutional Review Board/Ethics Committee

This study is being conducted under a United States Investigational New Drug application or other Clinical Trial Application, as appropriate. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB/EC. This board must operate in accordance with current local, regional, and federal regulations. The investigator will send a letter or certificate of IRB/EC approval to Exelixis (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

### 10.4 Compliance with Trial Registration and Results Posting Requirements

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

### 10.5 Future Use of Subject Samples

. Samples that are being collected for research purposes will be used for this study, and they will not be banked for use on future, yet undetermined studies.

## 11 CONDITIONS FOR MODIFYING THE PROTOCOL

### 11.1 Emergency Modifications

The sponsor-investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. As soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to the IRB for review and approval.

### 11.2 Other Protocol Deviations/Violations

If a deviation or violation occurs, the deviation should be reported in OnCore®. Any protocol violation that occurs must be reported to the IRB per institutional policies and reported to IUSCC as soon as possible. IUSCC will determine if the violation affects the safety of the study subject and integrity of the data.

### 11.3 Amendments

If it is necessary for the study protocol to be amended, the amended protocol will be generated by IUSCC and must be approved by the FDA (if applicable) and the IRB prior to implementation. Local requirements must be followed.

The Principal Investigator is responsible for the distribution of these documents to the IRB, and to the study's research staff. The distribution of these documents to the regulatory authority will be handled according to local practice.

# 12 CONDITIONS FOR TERMINATING THE STUDY

Exelixis reserves the right to terminate the study, and investigators reserve the right to terminate their participation in the study, at any time. Should this be necessary, Exelixis and the investigator will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Exelixis and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

# 13 STUDY DOCUMENTATION AND RECORD KEEPING

## 13.1 Investigator's Files and Retention of Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories as follows: (1) the investigator's study file, and (2) subjects' clinical source documents.

The investigator's study file will contain the protocol and protocol amendments, CRFs, query forms, IRB/EC and governmental approvals with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subjects' clinical source documents include the subjects' hospital/clinic records; physicians' and nurses' notes; the appointment book; original laboratory, ECG, electroencephalogram, X-ray, pathology and special assessment reports; signed informed consent forms; consultant letters; and subject screening and enrollment logs.

The investigator must keep these two categories of documents on file for at least the latest of 2 years following the marketing application approval date for the study treatment in the indication being investigated, 2 years after the investigation is completed or discontinued, or for a time consistent with local regulatory requirements. After that period, the documents may be destroyed subject to local regulations with prior written permission from Exelixis. If the investigator wants to assign the study records to another party or move them to another location, Exelixis must be notified in advance.

If the investigator cannot guarantee the archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Exelixis to store these in a sealed container outside of the study site so that they can be returned sealed to the

investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

### 13.2 Source Documents and Background Data

Upon request, the investigator will supply its licensees and collaborators with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

### 13.3 Audits and Inspections

The investigator should understand that source documents for this study should be made available, after appropriate notification, to qualified personnel from the Exelixis Quality Assurance Unit (or designee) or to health authority inspectors. The verification of the CRF data must be by direct inspection of source documents.

### 13.4 Case Report Forms and Data Submission

This study will utilize electronic Case Report Form completion in the OnCore® database. A calendar of events and required forms are available in OnCore® at https://cancer.iu.edu/oncore. The OnCore® database is a comprehensive database used by the Indiana University Simon Cancer Center (IUSCC) Clinical Trials Office (CTO) and supported by the Indiana University Simon Cancer Center. Access to data through OnCore® is restricted by user accounts and assigned roles. Once logged into the OnCore® system with a user ID and password, OnCore® defines roles for each user which limits access to appropriate data.

All source documents are to remain in the patient's clinic file. All documents should be kept according to applicable federal guidelines. Clinical trial data in OnCore® are periodically monitored by the IUSCC per the Data Safety Monitoring Committee (DSMC) Charter (see Section 9.1.1).

All paper forms should be typed or filled out using indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his or her authorized delegate.

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data in the CRFs and in all required reports.

## 14 CONFIDENTIALITY OF TRIAL AND SUBJECT RECORDS

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents, subjects should be identified by identification codes and not by their names. The investigator should keep a subject enrollment log showing codes, names, and addresses. The investigator should maintain documents not for submission to Exelixis or designees (e.g., subjects' written consent forms) in strict confidence.

All tumor scans, research samples, photographs, and results from examinations, tests, and procedures may be sent to Exelixis and its partners or designees for review.

## 15 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The Principal Investigator (Protocol Chair) holds the primary responsibility for publication of the study results; provided that the PI will provide any such publication to Exelixis, Inc. for review at least sixty (60) days before submission and also comply with any provisions regarding publication that are agreed to between the PI's institution (e.g., institution name) and Exelixis, Inc. in the Clinical Trial Agreement related to this study. The results will be made public within 24 months of the end of data collection. However, if a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. In any event, a full report of the outcomes should be made public no later than three (3) years after the end of data collection. Authorship for abstracts and manuscripts resulting from this study will be determined in accordance to guidelines established by the International Committee of Medical Journal Editors.

## 16 REFERENCES

1. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2007;25:1960-6.

2. Troiani T, Martinelli E, Capasso A, et al. Targeting EGFR in pancreatic cancer treatment. Current drug targets 2012;13:802-10.

3. Bryant KL, Mancias JD, Kimmelman AC, Der CJ. KRAS: feeding pancreatic cancer proliferation. Trends in biochemical sciences 2014;39:91-100.

4. Raponi M, Winkler H, Dracopoli NC. KRAS mutations predict response to EGFR inhibitors. Current opinion in pharmacology 2008;8:413-8.

5. Navas C, Hernandez-Porras I, Schuhmacher AJ, Sibilia M, Guerra C, Barbacid M. EGF receptor signaling is essential for k-ras oncogene-driven pancreatic ductal adenocarcinoma. Cancer cell 2012;22:318-30.

6. Di Renzo MF, Poulsom R, Olivero M, Comoglio PM, Lemoine NR. Expression of the Met/Hepatocyte Growth Factor Receptor in Human Pancreatic Cancer. Cancer Research 1995;55:1129-38.

7. Jo M, Stolz DB, Esplen JE, Dorko K, Michalopoulos GK, Strom SC. Cross-talk between Epidermal Growth Factor Receptor and c-Met Signal Pathways in Transformed Cells. Journal of Biological Chemistry 2000;275:8806-11.

8. Puri N, Salgia R. Synergism of EGFR and c-Met pathways, cross-talk and inhibition, in non-small cell lung cancer. Journal of carcinogenesis 2008;7:9.

9. Brandes F, Schmidt K, Wagner C, et al. Targeting cMET with INC280 impairs tumour growth and improves efficacy of gemcitabine in a pancreatic cancer model. BMC cancer 2015;15:1064.

10. Reckamp K, Frankel P, Mack P, Gitlitz B et al. Phase II trial of XL184 (cabozantinib) plus erlotinib in patients (pts) with advanced EGFR-mutant non-small cell lung cancer (NSCLC) with progressive disease (PD) on epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy: A California Cancer Consortium phase II trial (NCI 9303). J Clin Oncol (Meeting Abstracts) May 2014 vol. 32 no. 15_suppl 8014

11. Wang-Gilliam A, Li C, Bodoky G et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet. 2015 Nov 29. pii: S0140-6736(15)00986-1.

12. Torino F, Corsello SM, Longo R, Barnabei A, Gasparini G. Hypothyroidism related to tyrosine kinase inhibitors: an emerging toxic effect of targeted therapy. Nat Rev Clin Oncol. 2009;6(4):219-28.

13. Wright JR, Ung Y, Julian J, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. J Clin Oncol. 2007;25:1027-32.

# 17 APPENDICES

## 17.1 Appendix A: Performance Status Criteria

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

ECOG, Eastern Cooperative Oncology Group