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Pilot Study of EGFR Inhibition with Erlotinib in Cirrhosis to Inhibit Fibrogenesis and Prevent Hepatocellular Carcinoma

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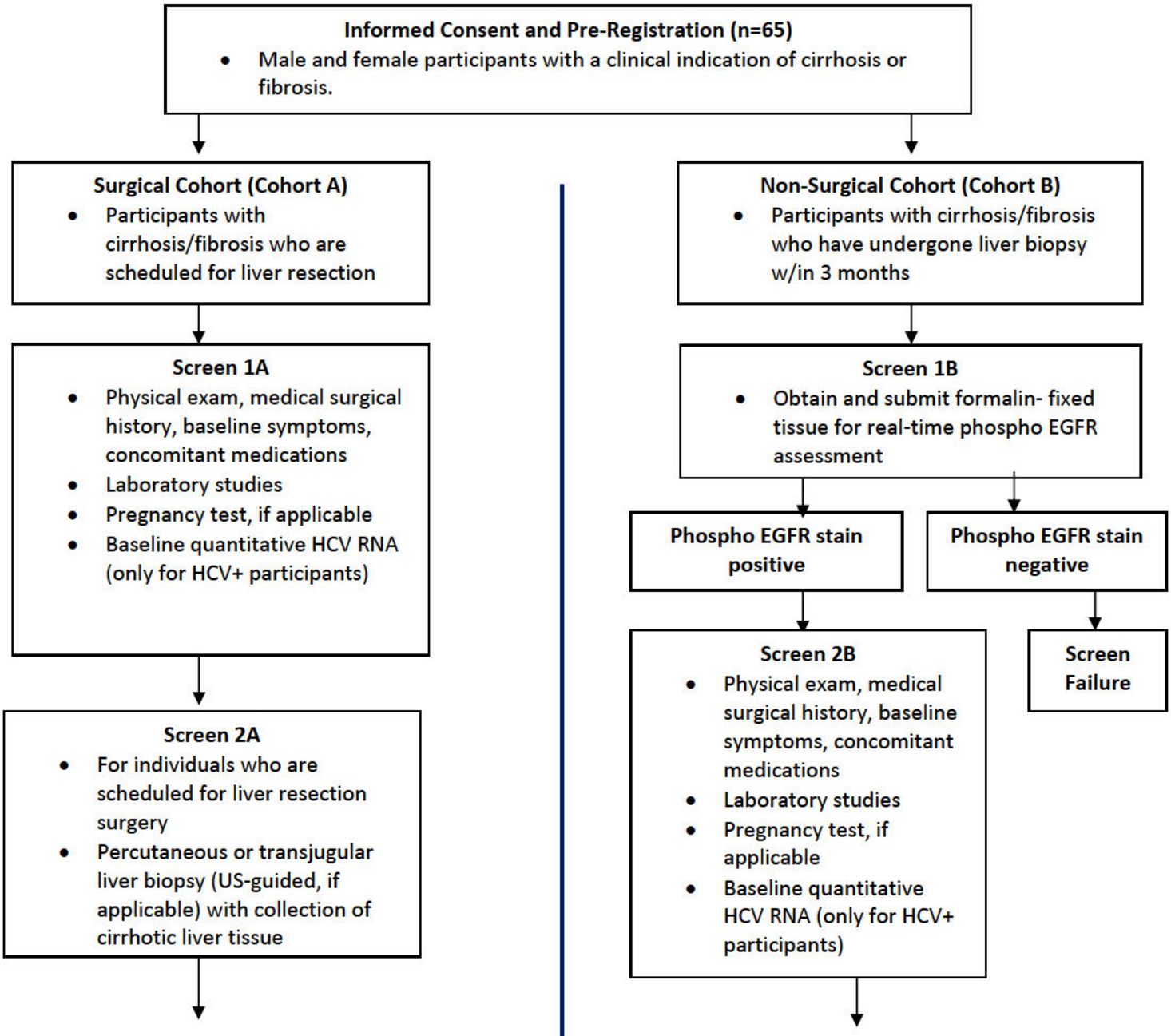
Pilot Study of EGFR Inhibition with Erlotinib in Cirrhosis to Inhibit Fibrogenesis and Prevent Hepatocellular Carcinoma

SCHEMA

Prior to discussing protocol entry with the participant, call the CPN Registration Office (507-284-4130) between 8:00 a.m. and 4:30 p.m. Central Time to insure that a place on the protocol is open to the participant.



Registration and Assignment to a Dose Level Group (n-45)
(This accounts for screen failures from the non-surgical cohort as well as other screen failures from the surgical cohort (approximately 30%)

Intervention

- Daily erlotinib x 7 days at assigned dose (5-14 days is the acceptable range for being considered evaluable). See Section 3 for detail concerning how treatment arms and expansion cohort will be assigned.
    - Dose level +2 = 150 mg/day
    - Dose level +1 = 100 mg/day
    - Dose level 0 = 75 mg/day (starting dose level)
    - Dose level -1 = 50 mg/day
    - Dose level -2 = 25 mg/day

Post-intervention Evaluation

Timeframe: May begin on the day prior to surgery (surgical cohort A only); must be complete before administration of anesthesia on the day of surgery (surgical cohort A) or biopsy (non-surgical cohort B).

1. Physical exam, WIWI Questionnaire
2. Final AE Assessment
3. Final dose of erlotinib (on the day of surgery before blood is drawn for labs and research)
4. Repeat laboratory studies and research blood draw (prior to anesthesia)

Collection of Post-Intervention Data and Specimens

- Collection of portion of resected liver (non-tumor bearing tissue ≥ 1 cm from negative margin for surgical cohort A) or tissue from liver biopsy (non-surgical cohort B) for biomarker assessment and endpoint evaluation.

Endpoint: To find the safe and minimum effective dose (MED) that achieves at least a 40% response rate, where a response is defined as an evaluable participant that achieves a reduction of at least 50% from baseline in liver phospho-EGFR staining, defined as the percentage of positive pixels, after a 7-day intervention period with daily erlotinib.

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1. OBJECTIVES

Primary Objective: Determine the safe and minimum effective dose (MED) of daily erlotinib that inhibits epidermal growth factor receptor (EGFR) signaling in the target organ (liver) as assessed by phospho-EGFR staining.

Secondary Objective: Determine the relationship between erlotinib dose-schedule and side effects in participants with cirrhosis.

Translational Objectives:

1. Determine the relationship between erlotinib dose-schedule and immuno-histochemical staining pattern of phospho-ERK, proliferating cell nuclear antigen (PCNA), epidermal growth factor (EGF), and alpha Smooth Muscle Actin (αSMA) in the liver.
2. Determine the relationship between erlotinib dose-schedule and gene expression signature associated with prognosis in cirrhosis participants following hepatocellular carcinoma (HCC) resection.
3. Determine the relationship between erlotinib dose-schedule and viral load in participants with HCV+.
4. Determine the relationship between erlotinib dose-schedule and erlotinib plasma level on day of liver resection.

1.1 Primary Endpoint: To find the safe and minimum effective dose (MED) that achieves at least a 40% response rate, where a response is defined as an evaluable participant that achieves a reduction of at least 50% from baseline in liver phospho-EGFR staining, defined as the percentage of positive pixels, after a 7-day intervention period with daily erlotinib.

1.2 Secondary Endpoint: To assess the complete adverse event profile for erlotinib.

1.3 Translational/Exploratory Endpoints:

1. To assess the relationship between dose-level and staining of phospho-ERK, PCNA, EGF, and αSMA in the liver.
2. To determine the relationship between erlotinib dose-schedule and gene expression signature previously demonstrated to be associated with prognosis in cirrhosis patients following HCC resection.
3. To determine whether erlotinib is associated with a measurable reduction in viral load in participants with Hepatitis C (HCV+).
4. To determine the relationship between erlotinib dose-schedule and erlotinib plasma level on the day of liver resection.

2. BACKGROUND

2.1 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the sixth most common solid tumor worldwide, and due to its poor prognosis, it is the third-leading cause of cancer related death (1). Identification of high-risk populations suitable for screening and chemoprevention has been proposed as the most efficient strategy to abrogate HCC-related mortality (2). While the cause of HCC is multifactorial, the common pathway for

the majority of cases is cirrhosis. Accordingly, the clinical diagnosis of cirrhosis provides for a well-defined, high risk population of intervention with chemoprevention.

Epidermal growth factor (EGF) expression is associated with progression of cirrhosis (3), and in animal models, overexpression of EGF in liver tissue leads to formation of hepatocellular carcinoma (4, 5). In humans, a functional single nucleotide polymorphism (SNP) in the EGF gene is associated with an increase in EGF levels in liver tissue, and is also associated with increased risk for hepatocellular carcinoma (6). Among cirrhotic patients, those with high EGF expression in their liver tissue have the poorest overall survival. In animal models, inhibition of the EGF receptor (EGFR) with a tyrosine kinase inhibitor, erlotinib, inhibits and reverses hepatic fibrosis and reduces the rate of transformation to hepatocellular carcinoma (HCC) (7). Use of another EGFR inhibitor, gefitinib, in a rat model of cirrhosis also was associated with a reduction in HCC (8). Accordingly, blockade of EGFR with oral inhibitors presents a promising therapeutic approach to liver fibrosis and cirrhosis, as well as prevention of HCC. Further rationale for clinical evaluation of EGFR inhibition stems from the observation that because EGFR is a co-factor important for HCV entry into cells, EGFR tyrosine kinase inhibitors such as erlotinib have substantial antiviral activity (9).

2.2 Erlotinib (Tarceva®)

Erlotinib is a reversible tyrosine kinase inhibitor and acts on the EGF receptor EGFR. Erlotinib binds in a reversible fashion to the adenosine triphosphate (ATP) binding site of the receptor. Normal EGFR signaling involves ATP binding to an EGFR homodimer, following which tyrosine phosphorylation of the EGFR subunits occurs. The irreversible binding of erlotinib to EGFR prevents ATP binding and prevents this phosphorylation and subsequent signal transduction. Downstream signaling pathways include the Ras>Raf>MEK>ERK pathway.

Erlotinib is marketed for in the United States for lung cancer and pancreatic cancer. The agent has been clinically tested for activity against many other cancers, including hepatocellular carcinoma both as a single agent and combined with sorafenib. Plasma concentrations of erlotinib in smokers as compared to non-smokers are reduced. Common side effects experienced by cancer patients include rash, fatigue, anorexia, and diarrhea. Extremely rare side effects include interstitial lung disease; gastrointestinal perforation; bullous, blistering, or exfoliative skin conditions; and inflammatory conditions of the eye.

2.3 Rationale

Preliminary Data:

- Gene-expression profiles in patients with cirrhosis and resected HCC demonstrate that the surrounding non-tumoral liver tissues contain a gene expression signature that identifies those patients most likely to die from complications of cirrhosis (10). The 186-gene cirrhosis prognosis signature consists of a 73-gene poor-prognosis signature and 113-gene good-prognosis signature. This signature was developed in a training set of 82 Japanese patients and validated in a set of 225 patients from the U.S. and Europe. The EGF gene is a significant component of this signature, and those with high EGF expression in their liver tissue have worse survival (10).
- The EGF gene SNP 61*G (rs4444903) is a functional SNP. In cirrhosis patients, the number of G alleles correlates with serum and liver EGF levels; subjects with G/G genotype have higher EGF levels than those with G/A genotype, who have higher levels than those with A/A genotype. This SNP correlates with risk for HCC in cirrhosis patients: those with G/G genotype have a greater risk for

HCC than those with G/A genotype, who have a higher risk than those with A/A genotype. This correlation was confirmed in a set of patients from the U.S. and an independent set of European patients (11). We have collaborated with a group at Nagoya University and recently demonstrated that HCC risk correlates with the EGF SNP in a Japanese cirrhotic patient population.

- Subjects from the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial (n = 816) that were followed prospectively for development of HCC were analyzed for EGF SNP. Using a Cox proportional hazards model, the EGF SNP was found to correlate with risk for HCC. A prediction model was developed that includes the EGF genotype to identify patients at low, intermediate, and high risk for HCC; 6-year cumulative HCC incidences were 2.3%, 10.4%, and 26%, respectively (11).
- A rat model of progressive fibrosis and cirrhosis induced by repeated, low-dose diethylnitrosamine (DEN) was demonstrated to closely resemble the histopathologic, physiologic, and molecular features observed in human cirrhosis. A global human cirrhosis gene expression signature was developed by comparing 10 normal livers to 13 cirrhotic livers using a publicly available dataset (GEO accession number GSE6764). Strong enrichment of the human signature in the DEN-treated rat livers was observed, indicating that the rat model indeed recapitulates global transcriptional dysregulation observed in human cirrhosis. And EGF was demonstrated to activate hepatic myofibroblasts/hepatic stellate cells (HMF/HSC), which are the key effector cells that promote liver fibrogenesis.
- Administration of clinically-achievable doses of an EGF receptor (EGFR) antagonist erlotinib to rats with DEN-induced cirrhosis suppressed the EGFR pathway as assessed by measurements of phosphoEGFR and other downstream signals in the liver, decreased HMF/HSC activation, reduced fibrogenesis and prevented progression of cirrhosis and subsequent HCC (7). Histologic examination of liver sections stained by H&E and trichrome revealed a lesser severity of fibrosis and cirrhosis in erlotinib treated rats. The reduction of DEN-induced fibrogenesis associated with erlotinib was dose-dependent. Erlotinib-treated rats had significantly lower Ishak fibrosis scores compared to vehicle controls. Moreover, erlotinib reduced the score in some animals, indicating reversal of fibrosis. Erlotinib improved rat liver function as assessed by serum ALT, AST, alkaline phosphatase, total bilirubin, and glucose. The 73-gene poor-prognosis signature in erlotinib-treated vs. control animals was diminished in a dose-dependent fashion in response to erlotinib. Similarly, the 113-gene good-prognosis signature was increased in a dose-dependent fashion in erlotinib-treated vs. control animals.
- In addition to reducing fibrogenesis and improving liver function, erlotinib treatment significantly decreased the number of HCC tumors detectable at week 18 post DEN exposure. Control animals harbored 20.4 ± 5.5 tumors, whereas erlotinib at 2 mg/kg and 0.5 mg/kg harbored only 5.0 ± 2.2 (75% reduction). It should be noted that 0.5 mg/Kg is equivalent to the starting dose chosen for this Pilot study.
- Similar results were observed when CCL4–treated mice were exposed to either erlotinib or control vehicle.

These data demonstrate that erlotinib can inhibit fibrogenesis, improve liver function, and prevent HCC. Thus, blockade of EGFR with approved inhibitors presents a promising potential therapeutic approach to liver fibrosis and cirrhosis, as well as prevention of HCC. Prior to initiation of long-term clinical trials, it is critically important to determine the lowest dose of erlotinib that effectively inhibits EGFR in the target tissue. The results of this study are expected to define an optimal dose schedule for study of HCC prevention in subsequent randomized studies.

3. SUMMARY OF STUDY PLAN

This is a pilot study of erlotinib administered to participants with cirrhosis to determine the relationship between dose-schedule and reduction of phospho-EGFR immunostaining in the liver. All participants entered into this study must have a clinical diagnosis of liver fibrosis or cirrhosis. There will be two cohorts. Those in the surgical cohort (Cohort A) will have a clinical indication for liver resection. Participants will undergo a biopsy of cirrhotic liver for baseline phospho-EGFR staining, and then receive daily erlotinib for 7 days (range: 5-14 days) leading up to the morning of their scheduled liver resection. The resected liver will be analyzed for phospho-EGFR staining in comparison to baseline. Plasma levels of erlotinib on the day of operation will be obtained, which will allow for subsequent correlation between these levels and the reduction in liver phospho-EGFR staining in the event that the relationship between the erlotinib dose-schedule and phospho-EGFR staining is inconsistent.

The second cohort of participants (Cohort B) will include individuals who have had a liver biopsy clinically-indicated to assess fibrosis and cirrhosis within 3 months prior to pre-registration. Formalin-fixed tissue will be obtained and sent to Mayo Clinic Pathology Research Core (PRC) l for phospho-EGFR assessment. If the phospho-EGFR assessment is negative, the participant will be considered a screen failure and will not continue. If the phospho-EGFR assessment is positive, the participant will undergo additional screening for eligibility. Once deemed fully eligible, participants will receive daily erlotinib for 7 days (range: 5-14 days) leading up to the morning of their scheduled liver biopsy. Phospho-EGFR expression levels and plasma erlotinib levels will be compared pre- and post-intervention.

The surgical and non-surgical cohorts will be enrolled concurrently to meet the goal for evaluable participants at each dose level.

The first dose level will consist of an intermediate dose of erlotinib (75 mg/day). It was considered ideal to choose a starting dose with room for both escalation and de-escalation depending upon reported adverse events and efficacy. This starting dose is less than that prescribed for treatment of cancer (150 mg/day), and is the human equivalent of a dose demonstrated to have efficacy in a rat model of cirrhosis and HCC (7). If the end-point (reduction of phospho-EGFR staining) is not achieved at this initial dose level, and the dose level is deemed safe, the next dose level consists of a higher dose of erlotinib. Conversely, if the primary end-point is achieved at this initial dose level, and the dose level is deemed safe, then the next dose level consists of a lower dose of erlotinib. It is probable that this algorithm will determine the minimum effective dose (MED) with fewer participants than alternative algorithms of starting at the lowest dose and escalating, or starting at the highest dose and de-escalating. Once the minimum effective dose (MED) is defined by this algorithm, an expansion cohort of 20 (to obtain 10 evaluable participants) will be enrolled to improve statistical confidence of the observed response rate. See Section 13 for details on the study design and the endpoints. The maximum dose for this trial will be 150 mg/day, taking into account the observation that this dose level has proven safe in oncology patients, but simultaneously the side effects associated with this dose level are likely considered excessive for long term use as chemoprevention. See Sections 5.1 and 5.2 for dose level information. See Section 7.4.2 for description of determination of safe/maximum tolerated dose.

Participants will take erlotinib at their assigned dose level for 7 days (acceptable range = 5 days to 14 days) leading up to the morning of their scheduled liver resection or liver biopsy. Participants will be contacted by study personnel on the third day to obtain information on adverse effects and to ascertain compliance. If surgery or biopsy is delayed and treatment extends beyond 7 days, then an additional

phone call will be made between Day 6 and the day of surgery for AE assessment. Adverse events will be assessed approximately every three days during study intervention. An attempt will be made to contact the participant daily to remind him/her to take study medication and improve compliance. For purposes of the primary study endpoint (reduction in phospho-EGFR staining) it is important that participants continue the erlotinib up through the morning of their scheduled operation. Compliance with study agent administration will be documented through the use of a participant-completed medication diary.

For the surgical cohort (Cohort A), following liver resection, a portion of the resected liver will be studied for phospho-EGFR staining compared to staining obtained from the pre-intervention biopsy. For the non-surgical cohort (Cohort B), cores from the research liver biopsy following intervention will be compared with baseline staining obtained from a formalin-fixed tissue specimen as part of a previous clinically-indicated biopsy. These tissues will be studied for other secondary correlative science endpoints.

4. PARTICIPANT SELECTION

4.1 Pre-Registration Inclusion Criteria

4.1.1 Individuals with a clinical diagnosis fibrosis or cirrhosis of the liver (no more than Child-Pugh Classification A; Child-Pugh-Turcotte score of 6 or less) who have:

A. an indication for surgical liver resection, OR

B. a clinical liver biopsy (with research tissue specimens available for analysis) ≤ 3 months prior to pre-registration.

4.1.2 Age ≥18 years. Note: Because no dosing or adverse event data are currently available on the use of erlotinib (Tarceva®) in participants <18 years of age, children are excluded from this study but may be eligible for future pediatric trials, if applicable. There are no upper age limits as long as the individual is a candidate for surgical liver resection.

4.1.3 Willingness to discontinue smoking during the study two weeks prior to beginning the study and willingness to not smoke while taking study medication.

4.1.4 Not pregnant or breast feeding. Note: The effects of erlotinib (Tarceva ®) on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.

4.1.5 Willingness to use adequate contraception to avoid pregnancy or impregnation until 2 weeks after discontinuing study agent.

4.1.6 Willingness to provide mandatory blood specimens as specified in the protocol.

4.1.7 Able to undergo:

A. Percutaneous or transjugular biopsy of cirrhotic liver at least 7 days prior to liver resection (Surgical cohort), OR

B. A biopsy of the cirrhotic liver (Non-surgical cohort).

4.1.8 Willingness to authorize collection of tissue from surgically-resected liver or clinical liver biopsy for analyses specified in the protocol.

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

4.2 Pre-Registration Exclusion Criteria

4.2.1 Any prior treatment with erlotinib or other agent whose primary mechanism of action is known to inhibit EGFR.

4.2.2 Participants with a known diagnosis of HIV. Note: An HIV screening test does not have to be performed to evaluate this criterion.

4.2.3 Participants who regularly (≥ 2 times per week) use drugs that alter the pH of the GI tract, such as proton pump inhibitors (PPI) and antacids. Exceptions: Individuals who use prescription PPIs and have approval from their primary health care provider to discontinue for the duration of clinical trial participation may be enrolled. An alternate drug to control GERD/PUD symptoms will be suggested.

4.2.4 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements.

4.2.5 Use of potent CYP3A4 inhibitors, such as ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice.

4.2.6 Use of CYP3A4 inducers such as rifampicin, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital, and St. John's Wort.

4.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to erlotinib (Tarceva®).

4.2.8 Participants who cannot have their warfarin, Lovenox, Plavix, or other comparable medications held for percutaneous or transjugular liver biopsy and surgery if so indicated.

4.2.9 Non-surgical cohort only: Pathology report from clinical liver biopsy (≤ 3 months prior to pre-registration) demonstrates no histologic abnormalities associated with chronic hepatitis, steatohepatitis, fibrosis, or cirrhosis.

4.3 Registration Inclusion Criteria

4.3.1 ECOG performance status 0 or 1 (See Appendix A)

4.3.2 Participants must have normal organ and marrow function as defined below:

- INR ≤ 1.5

- Platelets ≥ 50 B/L (10^9/L)
- Total bilirubin ≤ 3 × institutional ULN
- AST (SGOT) and ALT (SGPT) ≤ 5 × institutional ULN
- Creatinine ≤ 1.5 × institutional ULN

4.3.3 Non-surgical cohort only: Positive phospho-EGFR assessment (≥100 stained pixels, see Section 7.3) from tissue obtained from previous clinical liver biopsy.

4.3.4 Pre-Intervention biopsy sample collected.

4.4 Registration Exclusion Criteria

4.4.1 Receiving any other investigational agents ≤6 months prior to Registration.

4.4.2 Surgical cohort (Cohort A only): Percutaneous or transjugular biopsy incomplete or not performed.

4.5 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial. The Participating Organizations (POs) were chosen, in part, based on access to the target participant population and access to potential participants of diverse backgrounds. Refer to each PO's Recruitment, Retention, and Adherence (RR&A) Plan for details.

4.6 Recruitment and Retention Plan

Each Participating Organization will be required to develop and submit a study- and site-specific RR&A plan for the purposes of insuring equal access to the clinical trial by individuals of all genders, races, and ethnic groups and for attaining the organization's accrual target. POs will use the RR&A Plan Template (Appendix C) as the basis for their plans. Each PO will be asked to provide a monthly accrual target. The CPN Operations team will monitor progress toward that target and request revised/corrective RR&A plans if necessary, RR&A plans will be reviewed annually, at a minimum.

In general, study teams will be identified by the site PI. With assistance from the CPN Operations Office, training in study implementation and roles in the RR&A plan will be provided by the site PI or designee. Potential participants will be identified by site study teams by review of medical charts and appointment schedules. Participant consent, screening, and study visits will be implemented per protocol and per institutional policies and procedures. Study teams will attempt to contact participants each day on study to improve compliance, retention, and adherence.

5. AGENT ADMINISTRATION

Intervention will be administered on an outpatient basis. Reported adverse events (AEs) and potential risks are described in Section 6.2.

5.1 Dose Regimen and Dose Groups

Once the date of their liver resection surgery (surgical cohort) or liver biopsy (non-surgical cohort) is established, participants will be assigned to a dose group and scheduled to take erlotinib once daily for 7 days including the day of surgery/biopsy. Recognizing that operative schedules sometimes change for medical and other reasons, the range of daily erlotinib that will be permitted is 5 to 14 days.

Dose level	Erlotinib dose
+ 2	150 mg/day
+ 1	100 mg/day
0 (starting level)	75 mg/day
- 1	50 mg/day
- 2	25 mg/day

5.2 Erlotinib (Tarceva®) Administration

Participants are provided with instructions to self-administer erlotinib orally each morning on an empty stomach at least one hour before or two hours after eating. Erlotinib will be administered via 25 mg tablets, such that for the following dose levels, the corresponding number of tablets will be taken each day:

DOSE	NUMBER OF 25 mg TABLETS
25 mg/day	1 tablet/day
50 mg/day	2 tablets/day
75 mg/day	3 tablets/day
100 mg/day	4 tablets/day
150 mg/day	6 tablets/day

If a study participant misses one dose, he/she should immediately notify the study coordinator, and then unless a previous dose has already been missed, he/she will be instructed to take the next dose as scheduled (e.g. do not double the dose the next day).

5.3 Run in Procedures: Not applicable

5.4 Contraindications

Food and grapefruit can raise the levels of erlotinib in your body and lead to increased side effects. Participants should avoid grapefruit, grapefruit juice, and products containing grapefruit juice (i.e. Fresca® and Squirt ®) unless instructed otherwise by their physician.

5.5 Concomitant Medications

Erlotinib may increase the effects of warfarin and cause bleeding complications. Although the duration of erlotinib in this study is short, participants that are on Coumadin (and similar anticoagulation medications) may need to have their INR checked as determined by their physician. Individuals who are on warfarin should begin "bridging therapy" at the time of study enrollment.

Cigarette smoking has been shown to reduce erlotinib exposure; therefore, smokers should be advised to stop smoking two weeks prior to starting the study and to continue not smoking while taking erlotinib.

Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and reduce its bioavailability. Co-administration of erlotinib with omeprazole, a proton pump inhibitor, decreased the erlotinib exposure and maximum concentration by 46% and 61%, respectively. Therefore, the concomitant use of proton pump inhibitors with erlotinib should be avoided when feasible.

5.6 Dose Modification

No dose modifications are permitted for this study, other than the dose escalations and de-escalations described in this protocol (See Section 7). Participants that experience ≥ Grade 3 AE will not receive further doses of erlotinib at any dose level.

5.7 Adherence/Compliance

5.7.1 Participants must have taken 85% of the scheduled doses (e.g. 6 out of 7 days) and must have taken the dose on the day of liver resection/biopsy (prior to liver resection/biopsy) to be considered evaluable for statistical purposes.
5.7.2 Methods used for monitoring adherence to the dose schedule will consist of a phone call interview every 3 – 4 days (no less frequent than twice per week) and review pill counts as recorded on medication diaries.

6. PHARMACEUTICAL INFORMATION

6.1 Erlotinib (Tarceva®; IND# [redacted]; IND Sponsor: NCI, DCP)

Clinical studies investigating the chemopreventive efficacy of erlotinib are conducted under IND [redacted] sponsored by NCI, DCP. Erlotinib (Tarceva®) is an epidermal growth factor receptor (EGFR) inhibitor approved by the FDA as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen. It is also indicated as first-line therapy for treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer in combination with gemcitabine.

Erlotinib drug product is manufactured as the hydrochloride (HCl) salt by Astellas Pharma Global Development, Inc. (Northbrook, IL; Astellas). Erlotinib is currently formulated as conventional, immediate-release tablets in 25 mg, 100 mg, and 150 mg strengths. For the purpose of this study, 25 mg strength tablets will be used. Erlotinib drug substance is an off-white to pale yellow powder. Conventional excipients in the formulation include lactose monohydrate, hypromellose, hydroxypropyl cellulose, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, magnesium stearate, and titanium dioxide.

6.2 Reported Adverse Events and Potential Risks

Over 50 Astellas (formerly OSI Pharmaceuticals, Inc.)-sponsored phase I, 2, and 3 clinical studies of erlotinib have been initiated or completed. Various doses and schedules of erlotinib as a single agent and in combination with conventional chemotherapy agents have been studied. Twelve phase I studies have been conducted in healthy volunteers to determine the safety, tolerance, pharmacology, and pharmacokinetics of erlotinib (n = 268). The phase I healthy subject experience is based on the use of different oral erlotinib doses and schedules ranging from single-dose administration of 1-1000 mg to administration of 200 mg twice daily (bid) compared with placebo. Early tolerability studies showed that 200 mg erlotinib bid was associated with dose-limiting rash and diarrhea in addition to reversible liver transaminase elevation. Subsequent single- or multiple-dose pharmacology studies of 100 or 150 mg erlotinib daily did not reveal any new safety findings; however, the characteristic acneiform rash was unacceptable in healthy participants receiving 150 mg erlotinib daily for approximately one week or longer.

The phase I experience in cancer patients includes studies with different erlotinib doses and schedules. The maximum tolerable dose (MTD) of single-agent erlotinib was determined to be 150 mg daily, with diarrhea being the dose-limiting toxicity (DLT) despite supportive antidiarrheal treatment. Weekly dosing of erlotinib up to 1600 mg did not define a MTD; however, severe drug-related skin disorders were reported for patients receiving 1400 and 1600 mg weekly.

The phase Ib studies were designed to evaluate the MTD and pharmacokinetics of erlotinib when combined with standard doses of common chemotherapy regimens. The patient populations in these trials in general consist of advanced, refractory cancer patients with limited therapeutic options. As expected, patients who received concomitant chemotherapy in each of these trials experienced more hematological toxicities, including anemia, neutropenia, and thrombocytopenia, than patients who received erlotinib as single-agent therapy. In a phase 2 trial of neoadjuvant erlotinib at 150 mg daily in invasive bladder cancer patients undergoing radical cystectomy, rash was the most common adverse event (AE), observed in IS patients (75%).

Other AEs, including fatalities, have been reported in patients receiving erlotinib for treatment of NSCLC, pancreatic cancer, or other advanced solid tumors, based on the safety evaluations of erlotinib in more than 1200 cancer patients who received erlotinib as monotherapy, more than 300 patients who received 100 or 150 mg erlotinib plus gemcitabine and 1228 patients who received erlotinib concurrently with other chemotherapies.

The most common AEs in patients receiving single-agent erlotinib at 150 mg for treatment of NSCLC in the 2nd/3rd line study were rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 9% and 6%, respectively, of erlotinib-treated patients. Rash and diarrhea each resulted in study discontinuation in I% of erlotinib-treated patients. Dose reduction for rash and diarrhea was needed in 6% and I% of patients, respectively. The median time to onset of rash was 8 days, and the median time to onset of diarrhea was 12 days. Liver function test abnormalities (including elevated alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin) were also observed. These elevations were mainly transient or associated with liver metastases. Grade 2 (>2.5-5.0 x ULN) ALT elevations occurred in 4% and <I% of erlotinib- and placebo-treated patients, respectively. Grade 3 (>5.0-20.0 x ULN) elevations were not observed in erlotinib-treated patients.

In the NSCLC maintenance study, the most common adverse reactions in patients receiving single-agent erlotinib at 150 mg were also rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 6% and 1.8%, respectively, of erlotinib-treated patients. Rash and diarrhea resulted in study discontinuation in 1.2% and 0.5% of erlotinib-treated patients, respectively. Dose reduction or interruption for rash and diarrhea was needed in 5.1% and 2.8% of patients, respectively. In erlotinib-treated patients who developed rash, the onset was within two weeks in 66% and within one month in 81%. Liver function test abnormalities (including elevated ALT, AST, and bilirubin) were also observed. Grade 2 (>2.5-5.0 x ULN) ALT elevations occurred in 2% and I%, and grade 3 (>5.0-20.0 x ULN) ALT elevations were observed in 1% and 0% of erlotinib- and placebo-treated patients, respectively. The erlotinib treatment group had grade 2 (> 1.5-3.0 x ULN) bilirubin elevations in 4% and grade 3 (>3.0-10.0 x ULN) in <I% compared with <1% for both grades 2 and 3 in the placebo group.

The most common AEs in pancreatic cancer patients receiving 100 mg erlotinib plus gemcitabine were fatigue, rash, nausea, anorexia, and diarrhea. In the erlotinib/gemcitabine arm, grade 3/4 rash and diarrhea were each reported in 5% of patients. The median time to onset of rash and diarrhea was 10 days and 15 days, respectively. Rash and diarrhea each resulted in dose reductions in 2% of patients and resulted in study discontinuation in up to I% of patients receiving erlotinib/gemcitabine. The 150 mg cohort was associated with a higher rate of certain class-specific AEs, including rash, and required more frequent dose reduction or interruption.

In the pancreatic carcinoma trial, 10 patients in the erlotinib/gemcitabine group developed deep venous thrombosis (incidence 3.9%), compared with three patients in the placebo/gemcitabine group (incidence 1.2%). The overall incidence of grade 3 or 4 thrombotic events, including deep venous thrombosis, was similar in the two treatment arms: 11% for erlotinib/gemcitabine *vs.* 9% for placebo/gemcitabine. No differences in grade 3 or 4 hematologic laboratory toxicities were detected between the erlotinib/gemcitabine and the placebo/gemcitabine groups. Grade 3 AEs in the erlotinib/gemcitabine group with incidences <5% included syncope, arrhythmias, ileus, pancreatitis, hemolytic anemia including microangiopathic hemolytic anemia with thrombocytopenia, myocardial infarction/ischemia, cerebrovascular accidents including cerebral hemorrhage, and renal insufficiency. Liver function test abnormalities (including elevated ALT, AST, and bilirubin) were also observed. The erlotinib/gemcitabine treatment group had grade 2 (>2.5-5.0 x ULN) ALT elevations in 31% and grade 3 (>5 .0-20.0 x ULN) elevations in 13% compared with 22% for grade 2 and 9% for grade 3 in the placebo/gemcitabine group.

There have been infrequent reports of serious interstitial lung disease (ILD)-like events, including fatalities, in patients receiving erlotinib for treatment of NSCLC, pancreatic cancer or other advanced solid tumors. In the randomized single-agent NSCLC study the incidence of ILD-like events was the same in both the placebo and erlotinib groups (0.8%). In the pancreatic cancer study (in combination with gemcitabine), the incidence of ILD-like events was 2.5% in the erlotinib/gemcitabine group *vs.* 0.4% in the placebo/gemcitabine group. The overall incidence of ILD-like events in approximately 32,000 erlotinib-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) was approximately 1.1 %. Reported diagnoses in patients suspected of having ILD-like events included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome, and lung infiltration. Symptoms started from five days to more than nine months (median 39 days) after initiating erlotinib therapy. In the lung cancer trials, most of the cases were associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, preexisting parenchymal lung disease, metatstatic lung disease, or pulmonary infections.

During NSCLC and combination pancreatic cancer trials, infrequent cases of gastrointestinal bleeding have been reported, some associated with concomitant warfarin or NSAID administration. These AEs were reported as peptic ulcer bleeding (gastritis, gastroduodenal ulcers), hematemesis, hematochezia, melena, and hemorrhage from possible colitis. Cases of acute renal failure or renal insufficiency, including fatalities, with or without hypokalemia have been reported. Cases of grade I epistaxis were also reported in both the single-agent NSCLC and the pancreatic cancer clinical trials. Corneal ulcerations or perforations have been reported in patients receiving erlotinib. Abnormal eyelash growth, including ingrowing eyelashes, excessive growth, and thickening of the eyelashes have been reported and are risk factors for corneal ulceration/perforation. Grade 3 conjunctivitis and keratitis have been reported infrequently in patients receiving erlotinib therapy in the NSCLC and pancreatic cancer clinical trials.

Hepatic failure has been reported in patients treated with single-agent erlotinib or erlotinib combined with chemotherapy in clinical studies and during postmarket use of erlotinib.

Bullous, blistering, and exfoliative skin conditions have been reported, including cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis. In patients who develop skin rash, the appearance of the rash is typically erythematous and maculopapular and it may resemble acne with follicular pustules, but is histopathologically different. This skin reaction commonly occurs on the face, upper chest, and back, but may be more generalized or severe (grade 3/4) with desquamation. Skin reactions may occur or worsen in sun-exposed areas; therefore, the use of sunscreen or avoidance of sun exposure is recommended. Associated symptoms may include itching, tenderness, and/or burning. Also, hyperpigmentation or dry skin with or without digital skin fissures may occur. Hair and nail disorders, including alopecia, hirsutism, eyelash/eyebrow changes (mentioned above), paronychia, and brittle and loose nails have also been reported.

In the pancreatic carcinoma trial, six patients (incidence 2.3%) in the erlotinib/gemcitabine group developed myocardial infarction/ischemia. One of these patients died due to myocardial infarction. In comparison, three patients in the placebo/gemcitabine group developed myocardial infarction (incidence 1.2%) and one died due to myocardial infarction. In the same trial, six patients in the erlotinib/gemcitabine group developed cerebrovascular accidents (incidence 2.3%). One of these was hemorrhagic and was the only fatal event. In contrast, there were no cerebrovascular accidents in the placebo/gemcitabine group. In the same trial, two patients in the erlotinib/gemcitabine group developed microangiopathic hemolytic anemia with thrombocytopenia (incidence 0.8%), compared with no patients in the placebo/gemcitabine group.

Cases of hepatorenal syndrome, acute renal failure (including fatalities), or renal insufficiency with or without hypokalemia have been reported. Some were secondary to severe dehydration due to diarrhea, vomiting, and/or anorexia while others were confounded by concurrent chemotherapy use. Asymptomatic increases in liver transaminases have been observed in erlotinib-treated patients. Rare cases of hepatic failure (including fatalities) have been reported during postmarketing use of erlotinib. Confounding factors for severe hepatic dysfunction have included pre-existing liver dysfunction from cirrhosis, viral hepatitis, hepatocellular carcinoma, hepatic metastases, or concomitant treatment with potentially hepatotoxic drugs.

Erlotinib can cause fetal harm when administered to a pregnant woman; therefore, women should avoid becoming pregnant while being treated with erlotinib. Adequate contraceptive methods should be used

during therapy and for at least two weeks after completing therapy. There are no adequate and well controlled studies in pregnant women using erlotinib; however, studies in animals have shown some reproductive toxicity. Breastfeeding should be discontinued during erlotinib therapy. While it is not known whether erlotinib is excreted in human milk, erlotinib and/or its metabolites were excreted in milk in animals.

Erlotinib is protein bound (92-95%) in humans and metabolized in the liver by cytochrome P450 (CYP)3A4, and to a lesser extent CYPIA2, and in the lungs by CYPIAI. A potential for drug-drug interaction exists when erlotinib is co-administered with drugs that are highly protein bound or that are potent CYP3A4 inhibitors/inducers. Potent inducers of CYP3A4 activity increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations, while potent CYP3A4 inhibitors increase exposure to erlotinib. For patients who are being concomitantly treated with a potent CYP3A4 inhibitor, a dose reduction should be considered in the presence of severe AEs. For patients who are being concomitantly treated with a potent CYP3A4 inducer, alternative treatments that lack potent CYP3A4-inducing properties should be considered. Potent CYP3A4 inhibitors include ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice. CYP3A4 inducers include rifampicin, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital, and St. John's Wort.

Cigarette smoking has been shown to reduce erlotinib exposure; therefore, smokers should be advised to stop smoking while taking erlotinib.

Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and reduce its bioavailability. Coadministration of erlotinib with omeprazole, a proton pump inhibitor, decreased the erlotinib exposure and maximum concentration by 46% and 61%, respectively; therefore, the concomitant use of proton pump inhibitors with erlotinib should be avoided.

Altered coagulation parameters and infrequent reports of bleeding events, including gastrointestinal and non-gastrointestinal bleeding, have been reported in patients in erlotinib clinical studies, some associated with concomitant warfarin administration. Patients taking warfarin or other coumarin-derivative anticoagulants should be closely monitored for changes in prothrombin time and International Normalized Ratio (INR).

6.3 Availability

Erlotinib will be provided to NCI, DCP by Astellas Pharma US for use in this study. Erlotinib will be handled and distributed by the NCI, DCP repository contractor MRI Global (Kansas City, MO).

6.4 Agent Distribution

Agents will only be released by NCI, DCP after documentation of IRB approval of the DCP-approved protocol and consent is provided to DCP and the collection of all Essential Documents is complete (see DCP website for description of Essential Documents). NCI, DCP-supplied agents may be requested by the Investigator (or their authorized designees) at each participating organization. DCP guidelines require that the agent be shipped directly to the institution or site where the agent will be prepared and administered. DCP does not permit the transfer of agents between institutions (unless prior approval from DCP is obtained). DCP does not automatically ship agents; the site must make a request. Agents are

requested by completing the DCP Clinical Drug Request form (NIH-986) (to include complete shipping contact information) and faxing or mailing the form to the DCP agent repository contractor:

John Cookinham, MRIGlobal, DCP Chemoprevention Agent Repository
1222 Ozark Street, North Kansas City, MO 64116
Phone: 816-360-3805
FAX: 816-753-5359
Email: NCI.DCP@mriglobal.org
Emergency telephone: 816-360-3800

6.5 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCP using the NCI Oral Drug Accountability Record Form (DARF). The Investigator is required to maintain adequate records of receipt, dispensing, and final disposition of study agent. This responsibility will be delegated to an appropriately trained individual at each Participating Organization, as listed on the Delegation of Tasks form.

Include on receipt record from whom the agent was received and to whom study agent was shipped, date, quantity and batch or lot number. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant.

The NCI Oral Drug Accountability Record (DARF) form is available on the CPN website at this location: http://cancerpreventionnetwork.org/sc.shtml

6.6 Packaging and Labeling

Erlotinib will be will be packaged, labeled and distributed by the NCI, DCP repository contractor. Erlotinib will be provided as 25 mg tablets.

6.7 Storage

Erlotinib tablets are supplied in bottles and should be stored in a secure location at temperatures between l5°C and 30°C (59°F and 86°F).

6.8 Pre-Registration and Registration

6.8.1 Pre-Registration

Prior to discussing protocol entry with the participant, call the CPN Registration Office (507-284-4130) between 8:00 a.m. and 4:30 p.m. Central Time to insure that a place on the protocol is open to the participant.

6.8.1.1 To pre- register a participant, the participating site will fax or email the completed Pre-Registration Eligibility Checklist to the CPN Registration Office (Fax: 507-284-0885) to pre-register all participants between 8:00 a.m. and 4:30 p.m. Central Time. Make sure the pre-registering investigator

has reviewed, signed, and dated the pre-registration eligibility checklist prior to submission. The CPN Registration Office will enter the data into the CPN-hosted database.

6.8.1.2 Participant ID numbers will be generated by the CPN Registration Application for assignment and will be assigned to the participant by the CPN Registration Office.

6.8.1.3 At the time of pre-registration, the CPN Registration Application will verify the following:

- IRB approval at the registering institution.
- Participant eligibility.
- Existence of a signed consent form.
- Existence of authorization for use and disclosure of protected health information (USA Institutions only).

6.8.1.4 The following will also be recorded:

- Participant has/has not given permission to collect and store blood and tissue for future use in research to learn about, prevent, treat, or cure cancer.
- Participant has/has not given permission to collect and store blood and tissue for future use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease).
- Participant has/has not given permission to send blood and/or tissue sample(s) to researchers at an outside institution.
- Participant has/has not given permission to his/her doctor (or someone from the Cancer Prevention Network) to contact them in the future to ask them to take part in more research.

6.8.1.5 Screening and on-study evaluations must be completed within the guidelines specified on the Schedule of Events.

6.8.1.6 All baseline symptoms must be documented and graded.

6.8.1.7 All participants will be automatically registered to the correlative components of this study (See Section 9).

6.8.1.8 All trial activities must be conducted at a CPN member institution under the supervision of a CPN physician.

6.8.2 Registration

6.8.2.1 To register a participant, the participating site will fax or email the completed Registration Eligibility Checklist to the CPN Registration Office (Fax: 507-284-0885) to register all participants between 8:00 a.m. and 4:30 p.m. Central Time. Make sure the registering investigator has reviewed, signed, and dated the registration eligibility checklist prior to submission. The CPN Registration Office will enter the data into the CPN-hosted database.

6.8.2.2 Intervention cannot begin prior to registration and must begin ≤ 14 days from registration.

6.8.2.3 Factors

Stratification Factors: None

Descriptive Factor:

- Dose Level : +2 vs. +1 vs. 0 vs. -1 vs. -2

Grouping Factor:

- Dose escalation/de-escalation cohort vs. Dose expansion cohort
- Cohort: Surgical vs. Non-surgical

6.9 Blinding and Unblinding

Not applicable.

6.10 Agent Destruction/Disposal

At the completion of investigation, all unused study agent will be returned to NCI, DCP Repository according to the DCP "Guidelines for AGENT RETURNS" and using the DCP form "Return Drug List." Destruction of returned and unused study agent is allowed with prior approval by MRIGlobal.

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events – Surgical Cohort A

Evaluation/ Procedure	Pre-Registration	Screen 1A[1]	Screen 2A	Registration	Days 1, 2, 4, and 5	Day 3[2] (+/-1)	Day 6 (+/-1) or Day Prior to Surgery	Post Intervention Evaluation	Collection of Post-Intervention Data and Specimens
Informed Consent	X								
Pre-Registration	X								
Registration				X[3]					
Medical/Surgical History		X							
Baseline Symptoms Assessment		X							
Physical Exam		X						X	
Vital Signs/ Height and Weight		X						X	
Laboratory Tests (HBV, HCV, INR, Total bilirubin, ALT, AST, BUN, Alk phos, Total protein, Albumin, CPK, Calcium, Creatinine, Quantitative HCV RNA [if HCV+])		X[14]						X[14,15]	
CBC with 5-part differential and platelets		X						X	
Research blood collection (including Plasma erlotinib)		X						X	
Pregnancy test, if applicable		X[4]			X[4]				
Liver biopsy with collection of normal tissue			X[5,6]						
Concomitant Medications		X				X	X	X	
Dispense Study Agent and Medication Diary				X					
Erlotinib Administration					X[7]	X	X	X[8,13]	
Collect Study Agent and Medication Diary								X[9]	

Evaluation/ Procedure	Pre-Registration	Screen 1A[1]	Screen 2A	Registration	Days 1, 2, 4, and 5	Day 3[2] (+/-1)	Day 6 (+/-1) or Day Prior to Surgery	Post Intervention Evaluation	Collection of Post-Intervention Data and Specimens
Was It Worth It Questionnaire								X[9]	
Collection of non-tumor bearing fresh tissue from resected liver									X
Adverse Events		X				X	X	X	
Telephone Contact					X[10]	X	X		

7.2 Schedule of Events – Non-Surgical Cohort

Evaluation/Procedure	Pre-Registration	Screen 1B[1]	Screen 2B[11]	Registration	Days 1, 2, 4, and 5	Day 3[2] (+/-1)	Day 6 (+/-1) or Day Prior to Biopsy	Post Intervention Evaluation	Collection of Post-Intervention Data and Specimens
Informed Consent	X								
Pre-Registration	X								
Obtain tissue from previous (≤ 3 months prior to pre-reg) liver biopsy and submit for phospho-EGFR evaluation		X[12]							
Medical/Surgical History			X						
Baseline Symptoms Assessment			X						
Physical Exam			X					X	
Vital Signs/ Height and Weight			X					X	
Laboratory Tests (HBV, HCV, INR, Total bilirubin, ALT, AST, BUN, Alk phos, Total protein, Albumin, CPK, Calcium, Creatinine, Quantitative HCV RNA [if HCV+])			X[14]					X[14,15]	
CBC with 5-part differential			X					X	

Evaluation/Procedure	Pre-Registration	Screen 1B[1]	Screen 2B[11]	Registration	Days 1, 2, 4, and 5	Day 3[2] (+/-1)	Day 6 (+/-1) or Day Prior to Biopsy	Post Intervention Evaluation	Collection of Post-Intervention Data and Specimens
and platelets									
Research blood collection (including Plasma erlotinib)			X					X	
Pregnancy test, if applicable			X[4]		X[4]				
Concomitant Medications			X			X	X	X	
Registration				X[3]					
Dispense Study Agent and Medication Diary				X					
Erlotinib Administration					X[7]	X	X	X[8,13]	
Collect Study Agent and Medication Diary								X[9]	
Was It Worth It Questionnaire								X[9]	
Collection of non-tumor bearing fresh tissue via liver biopsy									X
Adverse Events			X			X	X	X	
Telephone Contact					X[10]	X	X		

1. Screening activities (1A, 2A, and 2B) must take place after pre-registration and within 14 days prior to registration.
2. If treatment extends beyond 7 days, then another telephone contact, identical to the Day 3 contact, will take place between Day 6 and the day of surgery.
3. Within 30 days of registration, documentation (lab reports, clinical notes, etc.) of the following will be uploaded to the RAVE remote data capture application: Documentation of a diagnosis of fibrosis or cirrhosis (no more than Child-Pugh Classification A or Child-Pugh-Turcotte score of 6 or less); indication/eligibility for surgical liver resection (surgical cohort) or biopsy (non-surgical cohort); INR ≤ 1.5; Platelets ≥ 50 x 10^9/L; Total bilirubin ≤ 3 × institutional ULN; AST (SGOT) and ALT (SGPT) ≤ 5 × institutional ULN; Creatinine ≤ 1.5 × institutional ULN
4. Day 1 only: For women of childbearing potential only, a negative pregnancy test must be documented prior to initiation of study agent. This test does not have to be repeated on Day 1 if the first study agent dose is within 7 days of baseline test.
5. Liver biopsy must take place after pre-registration and after all other screening procedure, but before Registration.
6. For the Surgical cohort A only, submission of biopsy specimens is not required prior to registration/randomization. However, the CPN Pathology Coordinator, April Felt, must be notified that the pre-intervention biopsy did occur so that she can confirm readiness for registration.
7. First dose of erlotinib must take place ≤ 14 days after registration.
8. Final dose of erlotinib will be taken on the day of surgery/biopsy but before laboratory tests and before administration of anesthesia for surgery/biopsy.

9. Post-intervention evaluation may begin on the day prior to surgery/biopsy, if more convenient. If a clinical pre-surgery/pre-anesthesia evaluation takes place and the data are available, then it may replace the scheduled physical exam and vital sign assessment. Collection of study agent, medication diary, final AE assessment, and WIWI questionnaire may occur on the day prior to surgery/biopsy, the day of surgery/biopsy, or at the time of early termination as long as they are complete before administration of anesthesia for surgery/biopsy. Final dose of erlotinib must be taken with a sip of water before blood is drawn for labs and research and before administration of anesthesia for surgery/biopsy.
10. Study team will attempt to contact the participant by phone, text message, or email (per participant's preference) to remind them to take their study medication.
11. For non-surgical cohort, if phospho-EGFR assessment is negative, participant <u>will not</u> proceed to Screen 2B.
12. After informed consent and pre-registration, specimen from previous clinical biopsy will be obtained and submitted to Mayo Clinic for phospho-EGFR assessment (see Section 10.2.2.2).
13. To be eligible for the primary endpoint, study agent must be taken for 5-14 days (ideally 7 days), with final dose of study agent and post-intervention specimen collection taking place on the day of surgery/biopsy prior to blood tests and surgery/biopsy (ideally Day 7).
14. Reminder: The Quantitative RNA test for this study should be performed only if the HCV antigen test is positive.
15. HBV and HCV do not have to be repeated at Post-Intervention if they were negative/undetectable at Screening.

7.3 Screening/Baseline Testing/Prestudy Evaluation

Following informed consent, participants will be pre-registered to the study.

Participants in the surgical cohort will undergo a screening evaluation including blood chemistry (HBV, HCV, INR, Total bilirubin, ALT, AST, Alkaline phosphatase, BUN, creatinine, Creatine phosphokinase, Calcium, Total protein, Albumin, quantitative HCV RNA [if HCV+]), and hematology (CBC with 5-part differential, platelets). Blood will also be drawn for baseline levels for translational endpoints. Participants will undergo a history and physical, review of baseline symptoms, and review of concomitant medications. He/she will then undergo a percutaneous or transjugular liver biopsy of non-tumor-bearing liver to obtain study tissue for baseline analyses.

Participants in the non-surgical cohort will provide consent to obtain specimens from previous (≤ 3 months prior to pre-registration) clinical liver biopsy. Formalin-fixed specimens will be submitted to Mayo Clinic Pathology Research Core (PRC) for phospho-EGFR assessment. If the assessment is negative (< 100 stained pixels), the participant will be considered a screen failure and will not continue on-study. If the assessment is positive (≥ 100 stained pixels), participants will undergo additional screening evaluation including blood chemistry (HBV, HCV, INR, Total bilirubin, ALT, AST, Alkaline phosphatase, BUN, creatinine, Creatine phosphokinase, Calcium, Total protein, Albumin, quantitative HCV RNA [only if HCV+]), and hematology (CBC with 5-part differential, platelets). Blood will also be drawn for baseline levels for translational endpoints. Participants will undergo a history and physical, review of baseline symptoms, and review of concomitant medications.

If the participant meets all of the eligibility requirements, he/she will be registered to the study and assigned to a dose group.

7.4 Evaluation During Study Intervention

7.4.1 Study Intervention

Once the date of liver resection surgery (surgical cohort) or liver biopsy (non-surgical cohort) has been established, participants will receive a daily dose of erlotinib starting 6 days prior to the scheduled surgery/biopsy, including a 7^{th} dose on the morning of surgery/biopsy according to the dose level assigned at the time of registration. Intervention of 7 days is ideal, but participants receiving daily erlotinib for 5-14 days will be considered evaluable for endpoint assessment as long as they have taken 85% of scheduled doses and receive their final dose on the day of surgery/biopsy before the procedure.

Participants will be contacted by telephone on Day 3 (+/- 1 day) and Day 6 (+/- 1 day) for adverse event assessment, review of concomitant medications, and review of schedule of events for Days 3, 6 and 7. These assessments are required.

On days 1, 2, 4, 5, and all others that do not have scheduled study visits, the study team will attempt to contact the participant by telephone, text message, or email (per the participant's stated preference) to remind them to take their study medications. Voice mail messages may be left if allowed per institutional guidelines. These attempts will be documented in source documentation. It will not be considered a deviation if contact is not made.

Participants whose surgeries/biopsies are rescheduled and will take erlotinib for 10 to 14 days will be contacted one additional time between Day 6 and the day of surgery/biopsy for adverse event assessment, review of concomitant medications, and review of scheduled events.

7.4.2 Definition of Dose Limiting Toxicities (DLTs)
For adverse events deemed at least possibly related to study agent:

Toxicity	Definition
Rash	≥ Grade 4
All other AEs deemed at least possibly related to study agent	≥ Grade 3

Toxicities are based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4. All events that are deemed Serious Adverse Events will be reported within 24 hours of learning of the occurrence (See Section 11.2 for details).

Number of Participants with DLT at a Given Dose Level	Escalation Decision Rule
0 or 1 out of 5	Declare the dose level safe and follow the rules for determining minimum effective dose (MED).
2 or 3 out of 5	Enter 5 new participants at this dose level: • If, among all enrolled participants at this dose, the incidence of DLT is less than 33%, then declare the dose level safe and follow the rules for determining MED. • If, among all enrolled participants at this dose, the incidence of DLT is ≥ 33% then this dose is declared to be above the maximum tolerated dose (MTD) and the dose escalation is stopped, regardless of phospho-EGFR staining response. Declare the next lower dose the MTD if ≥ 5 participants have already been treated at that dose.
4 or 5 out of 5	Declare this dose to be above the MTD and de-escalate without further enrollment at this dose level.
If no DLTs are seen at any of the dose levels, then the MTD will be the maximum delivered dose. MTD will be defined as the highest safely administered dose at which < 33% of participants experience DLT **OR** no DLT is observed out of 5 participants at the maximum dose level, provided no DLT is observed at any of the previous dose levels.	

Evaluation of toxicity will occur at each participant contact point. All DLTs qualify as Serious Adverse Events and will be reported to the medical monitor within 24 hours (See Section 11.2). If a suspension in enrollment to evaluate toxicity is required, the medical monitor will contact the CPN Operations Office, who will communicate that information immediately to the CPN Registration Office and all participating organizations.

7.4.3 Dose Escalation/De-escalation

Enrollment will be temporarily suspended after every 5 participants to evaluate phospho-EGFR response. If all 5 participants are evaluable, the dose level has been deemed safe, and phospho-EGFR is inhibited (i.e., a response, see Section 13) in at least 40% of evaluable participants, then enrollment will

continue at the next lower dose. If there are < 5 evaluable based on phospho-EGFR staining and the DLTs are below the limits specified above, then 5 more will be enrolled at that dose level in an attempt to reach a total of at least 5 evaluable participants. If the total number of evaluable participants remains < 5 and the dose level is deemed safe, then 5 more participants will be enrolled at this same dose level.

At dose level 0, if fewer than 2 responses are observed (in the first 5 evaluable participants) and the dose level is deemed to be safe, 15 participants will be enrolled at the next higher dose level (+1). If at least 2 participants have a response in the first 5 evaluable at this dose level and the dose level is deemed to be safe, this dose level will be declared the MED and further study with this dose will be warranted. If fewer than 2 responses (in the first 5 evaluable) are observed at this dose level, 15 participants will be enrolled at the next higher dose level (+2). If at least 2 responses are observed (in the first 5 evaluable participants) at this dose level and the dose level is deemed to be safe, this dose level will be declared the MED and further study with this dose will be warranted. If fewer than 2 responses are observed at this dose level (in the first 5 evaluable participants), we may consider including additional dose levels, after discussion with the DCP medical monitor, to find the MED for this study.

The lowest dose level at which there are ≥ 5 participants and ≥ 40% of these evaluable participants demonstrate a phospho-EGFR response will be considered the minimum effective dose (MED).

Reopening to enrollment after a temporary closure will occur after consultation with the DCP medical monitor.

7.5 Evaluation at Completion of Study Intervention

The participant will undergo a brief physical exam with vital signs. If institutional standards of care include a physical exam and this information is available to the study team, then the clinical physical exam will suffice. This evaluation may occur on the day prior to surgery/biopsy or prior to administration of anesthesia on the day of surgery/biopsy. Any remaining study agent supply and completed medication diary will be collected. The final assessment of adverse events and recording of concomitant medications will occur during this evaluation. Participants will be asked to complete the Was It Worth It (WIWI) questionnaire.

The final dose of erlotinib will be taken on the day of surgery/biopsy (prior to the procedure) with a sip of water. After the final erlotinib dose and prior to surgery/biopsy, repeat research blood draw and laboratory evaluations including blood chemistry (HBV, HCV, INR, Total bilirubin, ALT, AST, BUN, Creatinine, Alkaline phosphatase, Creatine phosphokinase, Calcium, Total protein, Albumin, quantitative HCV RNA [only if HCV+], and hematology (CBC with 5-part differential, platelets). Note that HBV and HCV do not have to be repeated at the post-intervention evaluation if the screening test results were negative/undetectable.

7.6 Post-intervention Follow-up Period

Immediately following the liver resection operation or liver biopsy, portions of liver from the resected specimen will be collected and processed for study (See Section 10 for details).

7.7 Methods for Clinical Procedures

7.7.1 Pre-intervention

After informed consent and screening, and prior to initiation of erlotinib treatment, all surgical cohort participants will undergo a percutaneous or transjugularbiopsy of their cirrhotic/fibrotic liver in a non-tumor bearing area. Participants should remain NPO after midnight before the scheduled biopsy to allow for use of conscious sedation if indicated. Whether to perform the biopsy under local anesthesia or under conscious sedation will be at the discretion of the clinician performing the biopsy. For percutaneous biopsy a 16-gauge core is preferable; an 18-gauge core is acceptable. All participants will be monitored post-procedure according to institutional standards of good clinical practice, after which time they may be discharged to home. The biopsy may be conducted via transjugular approach or under ultrasound guidance as deemed appropriate and will consist of 4 samples, of which 2 will be placed in RNAlater (Qiagen), and two will be placed in formalin. All samples will be stored in a refrigerator. If the clinician performing a percutaneous biopsy is unable to obtain at least two (2) core biopsies safely (e.g. participant starts bleeding), the clinician should abort the attempt. The participant will be considered not evaluable.

After informed consent, specimens will be obtained from clinically-indicated liver biopsy for all non-surgical cohort participants. Formalin blocks or unstained slides will be obtained and submitted to the CPN Pathology Coordinator for accessioning. The Pathology Coordinator will submit them to Mayo Clinic Pathology Research Core (PRC) for phospho-EGFR assessment.

7.7.2 Post-Intervention

For surgical cohort participants, liver resection surgery and post-surgical observation should follow institutional standards of care and good clinical practice. After liver resection, a portion of the liver specimen that does not contain tumor and consists of at least 1 gram of liver tissue will be placed in RNAlater (Qiagen). One other section of non-tumor bearing liver tissue measuring at least 1 cm x 1 cm x 0.5 cm will be placed in formalin and stored in the refrigerator.

Non-surgical cohort participants will undergo a post-intervention percutaneous or transjugular biopsy of their cirrhotic/fibrotic liver in a non-tumor bearing area. Participants should remain NPO after midnight before the scheduled biopsy to allow for use of conscious sedation if indicated. Whether to perform the biopsy under local anesthesia or under conscious sedation will be at the discretion of the clinician performing the biopsy. For percutaneous biopsies, a 16-gauge core is preferable; an 18-gauge core is acceptable. All participants will be monitored post-procedure according to institutional standards of good clinical practice, after which time they may be discharged to home. Percutaneous biopsy may be conducted under ultrasound guidance. Whether by perctuaneous or transjugular approach, biopsies will consist of a minimum of 2 samples. Four (4) samples is preferable. The first two samples will be placed in formalin. The second two will be placed in RNAlater (Qiagen). The four samples will be stored in a refrigerator. If the clinician performing a perctuaneous biopsy is unable to obtain the first two core biopsies safely (e.g. participant starts bleeding), the clinician should abort the attempt. The participant will be considered not evaluable.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Primary Endpoint

To find the safe and minimum effective dose (MED) that achieves at least a 40% response rate, where a response is defined as an evaluable participant that achieves at least a 50% reduction in liver phospho-EGFR staining, defined as the percentage of positive pixels, from baseline after a 7-day intervention period with daily erlotinib. See Section 13.6 for definition of evaluability for this endpoint.

8.2 Secondary Endpoint

- To assess the overall adverse event profile for erlotinib.

8.3 Translational/Exploratory Endpoints:

- To assess the relationship between dose-level and staining of phospho-ERK, PCNA, EGF, and αSMA in the liver
- To assess relationship between dose and modulation of a gene expression signature associated with prognosis in cirrhosis.
- To determine whether erlotinib is associated with a measurable reduction in viral load in participants with HCV+.
- To determine the relationship between erlotinib dose-schedule and erlotinib plasma level on the day of liver resection.

8.4 Off-Agent Criteria

Participants may stop taking the study agent due to: completion of the planned intervention period, development of an adverse event or serious adverse event, inadequate agent supply, noncompliance, use of concomitant medications, medical contraindication, refusal, ineligibility (see Section 8.5), major treatment violation (see Section 8.5) or alternative treatment. Participants will continue to be followed, if possible, for safety according to the intended schedule of events (see Section 7).

Participants discontinuing the planned intervention prematurely will be encouraged to complete the Post-Intervention Evaluation tests and procedures as appropriate (if participant does not refuse, is not lost to follow-up, or unless it is clinically contraindicated). See Section 8.5 for further details as to data submission for participants deemed Ineligible after starting treatment or classified as a Major Treatment Violation (i.e., protocol requirements regarding intervention during the first week post-randomization were severely violated).

8.5 Off-Study Criteria

Participants may go “Off-Study” for the following reasons: development of an adverse event or serious adverse event, death, lost to follow-up, participant withdrawal, physician decision, protocol violation, complete study, or other (with detailed comments provided). Reason(s) will be noted in the participant’s research records, with the primary reason clearly identified. The participant will be classified as (Off Study/Off Agent). Data submission and follow-up after participants are determined to be “Off-Study/Off-Agent” for specific situations is noted below:

A registered participant is deemed ineligible if the participant did not satisfy each and every eligibility criterion at the time of study entry, for example, identified based on an audit or through the case evaluation process.

- If participants received study intervention, on-study materials and all data up until the point of confirmation of ineligibility will be submitted.
- If participants did not receive study intervention, on-study materials must be submitted. No further data submission is necessary. No follow-up is required.

Major Treatment Violation: A registered participant is deemed as being in major treatment violation by the coordinating center, if the participant's very first treatment/intervention administration is so grossly administered in error, that the participant's data can no longer be used for the primary endpoint. These cases are typically rare.

- On-study material and all data up until the point of confirmation of a major violation must be submitted.

Cancel/Participant Withdrawal: A registered participant is deemed a cancel if he/she refuses the study or withdraws consent before any study intervention is given. On-study material must be submitted. The Off Study case report form must be submitted. No follow-up is required.

8.6 Study Termination

NCI, DCP as the study sponsor has the right to discontinue the study at any time. The FDA also has the ability to discontinue the study at any time.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Rationale for Methodology Selection

Gene signature assay: A total of 200ng RNA will be analyzed for the 186-gene liver signature by using nCounter Digital Analyzer system (NanoString) at the UT Southwestern/Simmons Cancer Center shared core facility. A scanned profile with median transcript count <100 will be regarded as having poor quality, and excluded from subsequent analysis. Scanned data will be normalized by scaling the transcript counts with geometric mean of built-in normalization genes by using NanoString normalizer module implemented in GenePattern genomic analysis toolkit (15). Suppression of the 186-gene signature will be quantitatively evaluated for each patient by comparing the paired specimens obtained before and 7 (5-14) days after starting the erlotinib treatment using nearest template prediction algorithm (14) implemented in GenePattern genomic analysis toolkit. A prediction of good prognosis with prediction confidence p-value <0.05 for the day 7 specimen will be regarded as statistically significant suppression of the gene signature in response to the erlotinib treatment.

Assessment of phospho-EGFR staining: Whole slide high-resolution imaging will be performed on the pre-and post-treatment biopsy slides/samples (Aperio, Leica Microsystems Inc. Buffalo Grove, IL 60089 United States). The Positive Pixel Count algorithm will be used quantify the amount of the positive staining on the pEGFR preparation (http://cancerpreventionnetwork.org/sc.shtml) three intensity ranges (220-175, 175-100, and 100-0). Only pixels with the strongest intensity (100-0) will be chosen for analysis. Pixels which are stained, but do not fall into the positive-color specification will be considered as negative stained pixels—these pixels will be counted and the fraction of positive pixels to total pixels will be determined. A pseudo-color markup image generated by the algorithm will be examined allowing for confirmation that the desired color and intensity ranges are recorded. Only hepatocytes will

be evaluated and portal tracts will be excluded from analysis. A meaningful reduction in the phospho-EGFR staining is defined as a 50% reduction in positive pixel to total pixel ratio relative to pre-erlotinib baseline.

If multiple specimens from a single participant are analyzed, the specimens showing the most significant reduction in percentage of positive pixels in response to erlotinib will be used for analysis. The rationale is that this pilot study is looking for evidence of a signal (i.e. a reduction in phospho-EGFR staining that indicates an effect on the pathway).

- Cell lines and/or tissue that are positive and negative for phospho-EGFR will serve as a positive and negative control.
- Allowable formalin fixation time for needle biopsy specimens: 4 to 24 hours
- Allowable formalin fixation time for resected liver specimens: 24 to 48 hours.
- All sections for staining should be cut at 10 microns.

In the nonsurgical cohort, positive **phospho-**EGFR assessment for initial eligibility will be defined as a minimum of 100 stained pixels.

For the immunohistochemical staining of paraffin-embedded liver tissues, the following antibodies will be used: phospho-EGFR:

- Cell Signaling - #2236 (mouse monoclonal). This detects phosphorylation at Tyr1068.
- phospho-ERK: Cell Signaling - #9101 (rabbit polyclonal) - which detects phosphorylation at Thr202/Tyr204
- PCNA: Cell Signaling - #2586 (mouse monoclonal)
- EGF: R&D Systems - #MAB236 (mouse monoclonal)
- αSMA: DakoCytomation #M0851 (mouse monoclonal). An alternative that has also been successful is Abcam #ab5694 (a rabbit polyclonal), which will be employed if necessary.

Note: Heavier or darker staining is commonly seen along the edges of IHC stained tissue sections. This is an artifact in the staining. Under the guidance of an Anatomic Pathologist, this artifact is avoided in selecting the analysis region for each slide.

9.2 Comparable Methods

For clinical translation as a prognostic biomarker, the 186-gene signature predictive of HCC risk was implemented in a Clinical Laboratory Improvement Amendments (CLIA)-compatible assay platform, nCounter assay (NanoString) specifically designed for clinical diagnostic laboratories (10). The assay platform has demonstrated minimal site-to-site variability in the gene expression measurements, indicating its suitability as a platform for clinical tests (12,13).

The primary options for analysis of efficacy with which erlotinib inhibits EGFR signaling in the liver are western blot, quantitative PCR, and immunohistochemical staining. In the clinical trial “A Phase IIa Randomized, Double-Blind Trial of Erlotinib in Inhibiting EGF Receptor Signaling in Aberrant Crypt Foci of the Colon” (NCT00754494), the EGFR signaling analysis conducted involved western blot analysis. The primary drawback of western blot and quantitative PCR analysis is the inability to distinguish the cell types contributing to any observed reduction in EGFR signaling. Based on the preliminary data described above, even though hepatocytes represent the dominant cell mass in the liver it is the stellate

cells in which EGFR signaling is targeted by erlotinib in this study. Only IHC has the capacity to distinguish cell type.

As stated in Section 7.6, if there is insufficient tissue for the primary endpoint (phospho EGFR staining), the participant will be considered not evaluable. If a radiologist can't get at least 2 (of 4) core biopsies safely for some reason (e.g. patient starts bleeding), they should abort their attempts.

10. SPECIMEN MANAGEMENT

10.1 Laboratories

Specimen analysis will take place at the laboratories listed below. Do not ship specimens to these laboratories. See Section 10.2.2.3 or the kit instructions for details on specimen shipment.

Research blood specimens:
Biospecimens Accessioning and Processing (BAP) Freezer
ST SL-16, 150 Third Street Southwest, Rochester, MN 55902
Telephone: 507-284-0163
Email: Thorson.ann@mayo.edu

IHC staining and analysis:
Mayo Clinic Pathology Research Core
Karla Kopp
2915 Valley High Drive NW
Rochester, MN 55901
Telephone: 507-266-5115
Email: kopp.karla@mayo.edu

Yujin Hoshida, MD, PhD
Director, Liver Tumor Translational Research Program
CPRIT Scholar in Cancer Research
Harold C. Simmons Comprehensive Cancer Center
Associate Professor of Medicine
Division of Digestive and Liver Diseases
Department of Internal Medicine
University of Texas Southwestern Medical Center
5323 Harry Hines Blvd
Dallas, TX 75390, USA
Phone: 1-214-648-6137
Email: Yujin.Hoshida@UTSouthwestern.edu
http://www.hoshida-lab.org

10.2 Collection and Handling Procedures

Research kits for shipping blood and tissue will be provided by BAP Kit Building (Biospecimen Accessioning and Processing Core Facility). Detailed collection, handling, labeling, packaging, and shipping instructions will be included with each kit. Participating Sites may obtain research kits by faxing

the Kit Supply Order Form to the number provided (found in the Forms Packet). At least two weeks should be allowed to receive the shipping kits. Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. They will not be forwarded by FedEx® rush delivery service unless the participating institution provides their own FedEx® account number. CPN will not cover the cost for rush delivery of kits.

Because charges are incurred for all outgoing kits, a small, but sufficient, supply of specimen collection kits should be ordered prior to participant entry.

10.2.1 Research Blood Specimens

Research blood will be drawn at baseline and after the final dose of erlotinib immediately prior to surgery. It will be processed according to the instructions in the blood specimen kit. Specimens will be processed (centrifuged, aliquoted, labeled per instructions in research blood kit), packaged, and shipped to BAP for accessioning and storage (See Section 10.1). Upon request, they will be shipped in batches for analyses.

10.2.2 Research Tissue Specimens

10.2.2.1 Surgical Cohort – Pre-Intervention
The pre-intervention percutaneous or transjugular liver biopsy may be conducted under ultrasound guidance following institutional standards of care before, during, and after the procedures. The collected specimens will consist of 4 specimens, of which 2 will be placed in RNAlater (Qiagen), and the other two will be placed in formalin. All four samples will be clearly labeled with study number, participant ID, specimen type, and date and time of collection. The RNAlater samples will be stored in a refrigerator at the participating site until shipped to the BAP Lab. The BAP Lab will store samples in a -80^{o}C freezer until sent to Dr. Hoshida's lab.

The formalin samples will be embedded in paraffin within 24 hours. The date and time of collection as well as paraffin embedding will be recorded on the Specimen Submission: Tissue case report form. Paraffin blocks will be shipped on a cool pack to the Mayo Clinic (CPN PC Office, address below) for accessioning. The PC office will forward blocks and cores to the Mayo Clinic PRC in one batch at the end of enrollment for each cohort.

10.2.2.2 Surgical Cohort – Post-Intervention
After the liver resection surgery, a portion of the liver specimen that does not contain tumor (≥ 1 cm from negative margin) and consists of at least 1 gram of liver tissue will be placed in RNAlater (Qiagen). One other section of non-tumor bearing liver tissue measuring at least 1 cm x 1 cm x 0.5 cm will be placed in formalin, clearly labeled, and stored in the refrigerator until shipment. The formalin samples will be embedded in paraffin within 24 hours.

Paraffin blocks will be shipped refrigerated to Mayo Clinic (CPN PC Office, address below) for accessioning and then forwarded to the Mayo Clinic PRC in one batch at the end of enrollment for each cohort.

If an institution cannot provide blocks, one 3 mm to 4 mm core should be taken from each block and placed into individual 2 mL tubes. Alternatively, sites may submit ten 5-micron slides plus one H&E.

Notes:

- For institutions that must, based on institutional policies, provide cores or slides instead of paraffin blocks: **Do not create the cores or cut slides until requested to do so by the CPN Pathology Coordinator.**
- Analysis for the study endpoints requires all slides for both time points for all participants to be sectioned at the same time.

The dates and times of collection, paraffin embedding, as well as sectioning will be recorded on the Specimen Submission: Tissue case report form to confirm compliance with these instructions.
All samples will be clearly labeled with study number, participant ID, specimen type, and date and time of collection.

Note: Sites are to notify CPN Pathology Coordinator (April Felt; felt.april@mayo.edu; 507-538-0268) when specimens are shipped for tracking purposes.

10.2.2.3 Non-Surgical Cohort – Pre-Intervention
After informed consent and pre-registration, specimens from the clinical biopsy (paraffin blockor ten []) 5-micron unstained slides and 1 H&E) will be obtained and submitted to the CPN Pathology Coordinator for assessioning. The pathology coordinator will ship immediately to Mayo Clinic PRC (Attention: Karla Kopp) for real-time (≤ 21 days from collection) phospho-EGFR assessment to determine eligibility. At this time, one or two slides will be cut from the block for the purposes of determining eligibility. The rest of the block will remain intact and be cut at the time of dose-level efficacy analyses (post-intervention). Results will be returned to CPN PC for entry into the database. If the assessment of the pre-intervention specimen is positive (See Section 7.3 for definition), the participant will be allowed to continue the screening process.

All samples will be clearly labeled with study number, participant ID, specimen type, and date and time of collection.

10.2.2.4 Non-Surgical Cohort – Post-Intervention

The post-intervention percutaneous or transjugular liver biopsy may be conducted following institutional standards of care before, during, and after the procedures. The collected specimens will consist of 4 samples. Two will be placed in RNAlater (Qiagen), and the other two will be placed in formalin. All specimens will be clearly labeled with study number, participant ID, specimen type, and date and time of collection. The RNAlater samples will be stored in a refrigerator at the participating sites until shipped to the BAP Lab. The BAP Lab will store samples in a -80^{o}C freezer until sent to Dr. Hoshida's lab (upon request).

The fresh formalin samples will be embedded in paraffin within 24 hours. The date and time of collection as well as paraffin embedding will be recorded on the Specimen Submission: Tissue case report form. Paraffin blocks will be shipped refrigerated to the Mayo Clinic (CPN PC Office, address below) for accessioning.

At the same time, the paraffin block containing the specimen used to establish initial eligibility at baseline will be submitted to the CPN PC Office. Additional sections are required because it is critical

that specimens used for efficacy analysis at the end of each dose level be cut for both time points and for all participants at the same time.

Institutions unable to submit paraffin blocks may submit one 3.0mm to 4.0mm core taken from each block and placed into individual 2mL tubes. If cores cannot be provided, cut one H&E and 10 sections at 5 microns and mount on charged slides.

Notes:

- For institutions that must, per institutional policies, provide cores or slides instead of paraffin blocks: **Do not create the cores or cut slides until requested to do so by the CPN Pathology Coordinator.** Analysis for the study endpoints requires all slides for both time points for all participants to be sectioned at the same time.
- **Note: Sites are to notify CPN Pathology Coordinator (April Felt; felt.april@mayo.edu; 507-538-0268) when specimens are shipped for tracking purposes.**

Post-intervention paraffin blocks (or cores) will be shipped from the CPN PC Office to the PRC at the Mayo Clinic in the same batch as the pre-intervention specimens at the conclusion of enrollment for each dose level.

Shipping Destination Summary:

Pre- and post-intervention paraffin blocks (or cores or unstained and H&E slides) will be shipped from all participating sites to:

CPN PC Office (Study MAY2013-02-02)
RO_FF_03_24-CC/NW Clinic
200 First Street Southwest, Rochester, MN 55905

Tissue specimens in RNALater and all research blood specimens will be shipped from all participating sites to:

Biospecimens Accessioning and Processing (BAP) Freezer
ST SL-16, 150 Third Street Southwest, Rochester, MN 55902

Specimens in RNAlater will be shipped from BAP to the Hoshida laboratory at the University of Texas Southwestern for further processing (See Section 10.1). Total RNA will be isolated by using RNeasy Kit (Qiagen) according to the manufacturer's instruction.

Specimen Collection Summary Chart

Specimen/ Collection tube (color of tube)	Mandatory or Optional	Volume to collect / tube or # of specimens to collect / visit	Blood product being processed	Screening	Post Intervention	Process at site?	Storage/ shipping conditions
Whole Blood/ No Additive (Red Top)	Mandatory	10 mL (1 tube)	Serum	X	X	Yes	Freeze at -20°C. or colder. Ship to BAP on dry Ice.
Whole Blood/ EDTA (Purple Top)	Optional	10 mL (1 tube)	Plasma, Buffy Coat*	X	X	Yes	Freeze at -20°C. or colder. Ship to BAP on dry Ice.
Whole Blood / Na Heparin (Green top)	Mandatory	10 mL (1 tube)	Plasma	X	X	Yes	Freeze at -20°C. or colder. Ship to BAP on dry ice for storage until end of study at which time they will be batched for plasma erlotinib analysis.
Liver Bx – Non tumor-bearing tissue	Mandatory	2 cores	-	X-surgical cohort	X-non-surgical cohort	Yes	Place in RNAlater, store in refrigerator (1-4°C), ship to BAP on cool pack.
Liver Bx – Non tumor-bearing tissue	Mandatory	2 cores	-	X-surgical cohort	X-non-surgical cohort	Yes	Place in formalin for 4-24 hours; embed in paraffin. Ship blocks cool pack to CPN PC Office.
Specimen from clinical liver biopsy	Mandatory	Block or slides		X-non-surgical cohort	X-non-surgical cohort		Ship block on a cool pack to CPN PC Office. Note that new sections will be created at the time of post-intervention efficacy analysis.
Liver resection specimen of non-tumor bearing tissue; ≥ 1 cm from negative margin	Mandatory	One 1-gram specimen	-		X-surgical cohort only	Yes	Place in RNAlater, store in refrigerator (1-4°C), ship to BAP on cool pack.
Liver resection specimen of non-tumor bearing tissue; ≥ 1 cm from negative margin	Mandatory	One 1-gram specimen	-		X-surgical cohort only	Yes	Place in formalin for 4-24 hours; embed in paraffin. Ship blocks on a cool pack to CPN PC Office.

***Buffy coat = White Blood Cells**

10.3 Shipping Instructions

The pre-addressed shipping labels will be provided with the specimen kits. Site teams are cautioned to make sure the correct specimen is sent to the correct location for analysis.

All sections of the requisition form and specimen collection labels must be completed and legible. All specimens should be sent over night (Monday through Friday) via FedEx® on cold packs. Samples shipped on Fridays must send an email with FedEx tracking number to the Biospecimen Resource Manager so arrangements can be made to stabilize the samples over the weekend. Exceptions for holidays will be communicated in advance to participating organizations. All samples must be shipped to the address provided on the specimen shippers and listed above (See Section 10.2.2).

All samples will be shipped in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations.

10.4 Tissue Banking

Biologic specimens collected during the conduct of each clinical trial that are not used during the course of the study will be considered deliverables under the contract and thus the property of the NCI.

At study completion, remaining frozen biologic specimens will be labeled (study number, participant ID number, specimen type, specimen number, date of collection) batched, and shipped (overnight, M-Th only) for banking/long term storage to:

Biospecimens Accessioning and Processing (BAP) Freezer
ST SL-16, 150 Third Street Southwest, Rochester, MN 55902

At study completion, all remaining paraffin blocks and slides will be labeled (study number, participant ID number, specimen type, specimen number, date of collection) batched, and shipped for banking/long term storage to:

CPN PC Office (Study MAY2013-02-02)
RO_FF_03_24-CC/NW Clinic
200 First Street Southwest, Rochester, MN 55905

NCI reserves the option to either retain or relinquish ownership of the unused biologic specimens. If NCI retains ownership of specimens, the Contractor shall collect, verify and transfer the requested biologic specimens from the site to a NCI-specified repository or laboratory at NCI's expense.

11. REPORTING ADVERSE EVENTS

DEFINITION: AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study.

Please note that all abnormal clinical laboratory values that are determined to be of clinical significance based on a physician's assessment are to be reported as AEs. Those labs determined to be of no clinical

significance or of unknown clinical significance (per the physician's assessment) should not be reported as AEs. Any lab value of unknown clinical significance should continue to be investigated/followed-up further for a final determination, if possible.

A list of AEs that have occurred or might occur (Reported Adverse Events and Potential Risks) can be found in §6.2, Pharmaceutical Information, as well as the Investigator Brochure or package insert.

11.1 Adverse Events

11.1.1 Reportable AEs

All AEs that occur after the informed consent is signed and baseline assessments are completed (including run-in) must be recorded on the AE CRF (paper and/or electronic) whether or not related to study agent.

11.1.2 AE Data Elements:

The following data elements are required for adverse event reporting.

- AE verbatim term
- System Organ Class (SOC)
- Common Terminology Criteria for Adverse Events v4.0 (CTCAE) AE term
- Event onset date and event ended date
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a serious adverse event (SAE)
- Whether or not the subject dropped due to the event
- Outcome of the event

11.1.3 Severity of AEs

11.1.3.1 Identify the AE using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.1. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs will be assessed according to the CTCAE grade associated with the AE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4.0. as stated below.

CTCAE v4.0 general severity guidelines:

Grade	Severity	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to AE.

ADL
*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.1.4 Assessment of relationship of AE to treatment

The possibility that the adverse event is related to study agent will be classified as one of the following: not related, unlikely, possible, probable, definite.

11.1.5 Follow-up of AEs

All AEs, including clinically significant lab abnormalities, will be followed according to good medical practices and documented as such.

11.2 Serious Adverse Events

11.2.1 DEFINITION: Fed. Reg. 75, Sept. 29, 2010 defines SAEs as those events, occurring at any dose, which meet any of the following criteria:

- Results in death
- Is life threatening (*Note: the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).*
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality/birth defect
- Important medical events that may not result in death, be life-threatening or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed.

The expected serious adverse events associated with the use of erlotinib (Tarceva ®) in previous clinical trials are described in Section 6.2. Because this clinical trial involves use of the erlotinib at significantly lower doses, the severity and frequency of AEs and SAEs are also expected to be lower.

11.2.2 Reporting SAEs to DCP

11.2.2.1 The Lead Organization and all participating Organizations will report SAEs on the DCP SAE form found at this location: http://cancerpreventionnetwork.org/sc.shtml

11.2.2.2 Contact the DCP Medical Monitor by phone or email within 24 hours of knowledge of the event.

Gary Della'Zanna, D.O., M.Sc.
National Institutes of Health, National Cancer Institute
Division of Cancer Prevention
9609 Medical Center Drive
Bethesda, MD 20892
Phone: 240-276-7042
Fax (with cover sheet, Attn: Dr. G. Della'Zanna): 240-276-7848
Email: dellazannagj@mail.nih.gov

Include the following information when calling the Medical Monitor:

- Date and time of the SAE
- Date and time of the SAE report
- Name of reporter
- Call back phone number
- Affiliation/Institution conducting the study
- DCP protocol number
- Title of protocol
- Description of the SAE, including attribution to drug and expectedness

11.2.2.3 The Lead Organization and all Participating Organizations will FAX or email written SAE reports in Word format to the DCP medical monitor within 48 hours of learning of the event using the DCP SAE form available at this location: http://cancerpreventionnetwork.org/sc.shtml

The written SAE reports will also be faxed or emailed to:

CPN Operations Office, Attn: CPN SAE Coordinator
Fax: 507-284-9628; Phone: 507-266-3128
E-mail: mcnamara.patricia@mayo.edu

Kenneth K. Tanabe, M.D., MAY2013-02-02 Study Chair
Fax: 617-724-3895; Phone: 617-724-3868
Email: ktanabe@partners.org

CCS Associates, DCP Regulatory Contractor
Fax: 650-691-4410; Phone: 650-691-4400
Email: safety@ccsainc.com

11.2.2.4 The DCP Medical Monitor and regulatory staff will determine which SAEs require expedited FDA submission. All SAES will be reported to the FDA in the IND annual report.

11.2.2.5 The Lead Organization and all Participating Organizations will comply with applicable regulatory requirements related to reporting SAEs to the IRB/REB/IEC.

11.2.3 Follow-up of SAE
Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the DCP SAE form in the appropriate format. Follow-up information should be sent to DCP as soon as available.

AEs and SAEs that are on-going at the time of the final AE assessment (post-intervention evaluation) will be treated according to institutional standards of good clinical practice.

12. STUDY MONITORING

12.1 Data Management

The Mayo Clinic Cancer Center database will be the database of record for the protocol and subject to NCI and FDA audit. Minimum Data Sets will be submitted to DCP per contract requirements. Please see 2012 CPN Master Data Management Plan.

12.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRF) utilizing NCI-approved Common Data Elements (CDEs). The approved CRFs will be used to create the electronic CRF (e-CRF) screens for data entry into the Mayo Clinic Cancer Center database. Amended CRFs will be submitted to the DCP Protocol Information Office for review and approval.

12.3 Source Documents

A source document is any document, form, or record where *specific participants'* data are first recorded. FDA [21 CFR 312.62 (b)] requires that the investigator "...prepare and maintain accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational agent or employed as a control in the investigation." Among many other items, source documents include:

- Inpatient and outpatient medical records
- Progress notes
- Consults
- Nursing notes
- Pathology reports
- Radiology reports
- Medicine/radiation administration records
- Surgical reports
- Laboratory reports
- Admission forms
- Flow sheets and worksheets that are signed and dated

- Protocol or study road maps
- Appointment books
- Participant diaries/calendars
- Blood and tissue collection/submission requisition forms (signed and dated).
- Case Report Forms (signed and dated):
    - Symptoms: Pre-Intervention
    - Physical Exam
    - Specimen Submission: Blood
    - Specimen Submission: Tissue

12.4 Data and Safety Monitoring Plan

The Master DSMP, applicable to all studies within the CPN Consortium provides detailed information regarding data and safety monitoring for this study. The trial will be monitored closely for occurrence of adverse events by the study team and by the Mayo Clinic Cancer Center Data Safety Monitoring Board (DSMB). The DSMB will be consulted regarding whether or not accrual should be suspended to allow for investigation in the occurrence of severe adverse events, particularly for those that are possibly, probably, or definitely related to the study agent.

12.5 Sponsor or FDA Monitoring

The NCI, DCP (or their designee), pharmaceutical collaborator (or their designee), or FDA may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study.

12.6 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, *etc*.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidances, and NCI/DCP requirements, unless the standard at the site is more stringent. The records for all studies performed under an IND will be maintained, at a minimum, for two years after the approval of a New Drug Application (NDA). For NCI/DCP, records will be retained for at least three years after the completion of the research. NCI will be notified prior to the planned destruction of any materials. The records should be accessible for inspection and copying by authorized persons of the Food and Drug Administration. If the study is done outside of the United States, applicable regulatory requirements for the specific country participating in the study also apply.

12.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

Not Applicable

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Description

This is a pilot study designed to assess the effect of erlotinib on participants with cirrhosis in trying to prevent hepatocellular carcinoma (HCC). The primary objective of this study is to determine the minimum effective dose (MED) of daily erlotinib that inhibits EGFR signaling in the target organ (liver) as assessed by phospho-EGFR staining. Statistical considerations regarding sample size are based on this primary study objective. Specifically, we will find the minimum effective dose (MED) that achieves at least a 40% response rate, **where a response is defined as a reduction of at least 50% in liver phospho-EGFR staining, defined as the percentage of positive pixels from baseline in an evaluable participant after a 7-day intervention period with daily erlotinib.**

The secondary endpoint of adverse events will assess the overall adverse event rates and specific adverse events for erlotinib over the 7 day intervention period. Translational endpoints are listed in Sections 1.3 and 8.3.

There is limited Quality of Life (QOL) data on participants who participate in chemoprevention trials and we intend to create a databank of QOL information by administering the "Was It Worth It" (WIWI) questionnaire at trial completion across multiple trials. We will seek to evaluate participant perception of their experience in trial participation once we have a reasonable amount of information (large enough sample size). Since participants who participate in these chemoprevention trials are high risk but otherwise healthy, the WIWI tool would help answer simple questions about participants' assessment of whether or not participation in this trial was "worth it."

13.2 Randomization/Stratification

Given that this is a single arm pilot trial of erlotinib, there will be no randomization or stratification.

13.3 Accrual and Feasibility

Ten participants will be enrolled (in cohorts of 5) at each dose level to reach the goal of 5 evaluable participants in each dose level using a cohorts-of-5 design. This assumes that 30%-40% of participants will not be evaluable for the primary endpoint for the surgical cohort, have no phospho-EGFR staining (i.e. no positive pixels, see Section 9.0) at baseline, for both cohorts, will otherwise be non-evaluable (drop-out, non-compliant etc.). Assuming that 10 participants are required at each dose level (to achieve the desired 5 evaluable participants), and assuming the theoretical maximum of 3 dose levels, a total of 30 participants may be required for the dose escalation phase to determine the MED. An additional 15 participants will be accrued to the MED in the expansion cohort, wherein we again assume that 30%-40% of participants will not be evaluable for the primary endpoint (see rational above), thus leading to 10 evaluable participants. See section 13.6 for the details on criteria for evaluability of primary endpoint. Thus, the maximum accrual to this trial may be 45 (30 for dose escalation and 15 for the expansion) in order to accrue 25 evaluable participants.

Update with Amendment 9: Because there were no dose-limiting toxicities and there were sufficient numbers of evaluable participants, none of the cohorts were repeated. The target accrual has been adjusted from the original "up to 65" downward to 31. The accrual time frame is limited due to the imminent expiration of the supply of study agent.

13.4 Primary Objective, Endpoint(s), Analysis Plan

The primary objective of this study is to determine a safe and minimum effective dose (MED) of daily erlotinib that inhibits EGFR signaling in the target organ (liver) as assessed by phospho-EGFR staining.

We have no data to demonstrate that this will be different between the surgical and non-surgical cohorts, thus the primary endpoint will be analyzed overall, including data from both cohorts.
The primary endpoint is to find the safe and MED that achieves a response rate of at least 40%, where a response is defined as an evaluable patient that achieves a 50% reduction in the percentage of positive pixels in the phospho-EGFR staining in the liver from baseline after a 7 day intervention period with daily erlotinib. See Section 13.6 for criteria for the evaluability of the primary endpoint.

Assuming a binomial distribution for the number of responses in 5 evaluable participants at a given dose level, and a true response rate of 60%, the probability of observing at least 2 responses is 91%. We felt this was adequate evidence of activity in a small pilot study (see table below with the details), given that a true response rate of 60% could not be ruled out even if we only observe a 40% response rate.

Number of responses (x)	P(x)
0	0.010
1	0.077
2	0.230
3	0.346
4	0.259
5	0.078

In summary, we will find the MED that achieves a 40% or higher observed response rate in participants that have at least some EGFR staining at baseline.

Once the MED is determined, we will expand accrual at that dose level to a total of 20 participants (to obtain 10 evaluable) to further evaluate the safety and response rate along with other translational endpoints at that dose level.

With 10 evaluable participants, we would be able to develop a 2-sided 90% confidence interval with a margin of error of about 25% for the response rate endpoint. Given that this is a pilot study, we would use the information we gain from the primary and secondary/translational endpoints to plan for a larger study that would further evaluate this treatment in this disease setting.

13.5 Secondary and Translational/Exploratory Endpoints

The secondary endpoint is to assess the complete adverse event profile for erlotinib.

Translational endpoints consist of the following:

- To assess the relationship between dose-level and staining of phospho-ERK, PCNA, EGF, and αSMA in the liver
- To assess relationship between dose and modulation of a gene expression signature associated with prognosis in cirrhosis.
- To determine whether erlotinib is associated with a measurable reduction in viral load in participants with HCV+.
- To determine the relationship between erlotinib dose-schedule and erlotinib plasma level on the day of liver resection.

Analysis Methods: The translational endpoints will be assessed from tissue samples. Data for these translational endpoints will be considered hypothesis generating and/or exploratory in nature. We will compare the baseline biomarker expression levels (e.g. staining of phospho-ERK, PCNA and αSMA; gene expression signature; viral load) across all the dose levels using analysis of variance (ANOVA) or the nonparametric equivalent. We will also assess the changes in these biomarker values from baseline to Day 7 using the Wilcoxon Signed-Rank test and compare these changes across dose levels using ANOVA (or the nonparametric equivalent). Graphical methods will also be used to assess the differences in these biomarker values across dose levels. All categorical variables will be analyzed using chi-square or Fisher's exact tests.

13.6 Reporting and Exclusions

To be evaluable for the primary endpoint, a patient needs to (1) meet the eligibility criteria, (2) receive erlotinib for 7 days (range 5-14 Days), (3) have EGFR staining at baseline in the surgical cohort (such that they could have a reduction in EGFR over the 7 day intervention period), (4) need their EGFR assessed post-baseline, and (5) taken 85% of the scheduled doses (6 of 7 days) and must have taken the dose on the day of liver resection (prior to liver resection surgery). Participants with erlotinib administration outside of the target duration will not be considered evaluable for the primary endpoint.

Sub-analyses for the different endpoints may be performed on the subsets of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of intervention, major protocol violations, etc.). However, sub-analyses will not serve as the basis for drawing conclusions concerning efficacy, and the reasons for excluding participants from the analysis will be clearly reported. There will be no imputation for missing data. A summary and listing of all major protocol violations will be provided. All details will be given in the final study report and/or manuscript. Participants lost to follow-up will be censored on the last date of assessment (or contact) and as appropriate for analyses that are dependent upon length of study participation.

13.7 Evaluation of Toxicity (Secondary endpoint)

All participants will be evaluable for adverse events (AEs) from the time of their first dose of erlotinib through completion of their post-intervention evaluation.

All AE analyses will be carried out at each dose level. The maximum grade for each type of adverse event will be recorded for each participant and frequency tables will be reviewed to determine the overall patterns. The number and severity of adverse events will be tabulated and summarized across all grades. Grade 3+ adverse events will be similarly described and summarized separately. As per NCI CTC Version 4.0, toxicities are defined as adverse events that are classified as either possibly, probably, or definitely related to the interventional agent. Overall toxicity incidence, as well as toxicity profiles will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses. In addition, we will review all adverse event data that are graded as 3, 4, or 5 and classified as either "unrelated or unlikely to be related to the study intervention in the event of an actual relationship developing.

13.7.1 Data and Safety Monitoring Plan

The trial will be monitored closely for occurrence of adverse events by the study team and by the Mayo Clinic Cancer Center Data Safety and Monitoring Board (DSMB) following the procedures established in the CPN Data and Safety Monitoring Plan.

See Section 7.3 for study-specific details related to review of adverse events for dose-limiting toxicities and closures to enrollment to evaluate safety.

If at any time a grade 5 adverse event is observed, the details of the event (such as relationship to study treatment) will be reviewed to determine whether study accrual should be suspended. We will also review all grade 4 adverse events regardless of attribution to monitor the emergence of any previously unrecognized treatment-related adverse events.

13.8 Evaluation of Response

Minimal Effective Dose (MED) determination (using dose levels defined in section 5.1)
In addition to assessment of responses discussed below, the dose-escalation/de-escalation decision will also depend on safety, see Section 7.3.

Ten participants will be enrolled at the starting dose level (dose level 0) and if at least 2 in the first 5 evaluable participants have a response (40%) and the dose level is deemed to be safe, 10 participants will be enrolled at the next lower dose level (-1). If at least 2 participants have a response in the first 5 evaluable at this dose level and this dose level is deemed to be safe, 10 participants will be enrolled at the next lower dose level (-2). If at least 2 responses are observed at this dose level as well (in the first 5 evaluable) and this dose level is deemed to be safe, then this dose level will be considered the observed MED for this study, and further study will be warranted at this dose level.

At dose level 0, if fewer than 2 responses are observed (in the first 5 evaluable participants) and the dose level is deemed to be safe, 10 participants will be enrolled at the next higher dose level (+1). If at least 2 participants have a response in the first 5 evaluable at this dose level and the dose level is deemed to be safe, this dose level will be declared the MED and further study with this dose will be warranted. If fewer than 2 responses (in the first 5 evaluable) are observed at this dose level, 10 participants will be enrolled at the next higher dose level (+2). If at least 2 responses are observed (in the first 5 evaluable participants) at this dose level and the dose level is deemed to be safe, this dose

level will be declared the MED and further study with this dose will be warranted. If fewer than 2 responses are observed at this dose level (in the first 5 evaluable participants), we may consider including additional dose levels to find the MED for this study.

13.9 Interim analysis: Not applicable

13.10 Ancillary Studies: Not applicable

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Form FDA 1572

Prior to initiating this study, the Protocol Lead Investigator at the Lead or Participating Organization(s) will provide a signed Form FDA 1572 stating that the study will be conducted in compliance with regulations for clinical investigations and listing the investigators, at each site that will participate in the protocol. All personnel directly involved in the performance of procedures required by the protocol and the collection of data should be listed on Form FDA 1572.

14.2 Other Required Documents

14.2.1 Signed and dated current (within two years) CV or biosketch for all study personnel listed on the Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.2 Current medical licenses (where applicable) for all study personnel listed on Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.3 Lab certification (*e.g.*, CLIA, CAP) and lab normal ranges for all labs listed on Form FDA 1572 for the Lead Organization and all Participating Organizations.

14.2.4 Documentation of training in "Protection of Human Research Subjects" for all study personnel listed on the FDA Form 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.5 Documentation of Federalwide Assurance (FWA) number for the Lead Organization and all Participating Organizations.

14.2.6 Signed Investigator's Brochure/Package Insert acknowledgement form

14.2.7 Delegation of Tasks form for the Lead Organization and all Participating Organizations signed by the Principal Investigator for each site and initialed by all study personnel listed on the form

14.2.8 Signed and dated NCI, DCP Financial Disclosure Form for all study personnel listed on Form FDA 1572 for the Lead Organization and all Participating Organizations

14.3 Institutional Review Board Approval

Prior to initiating the study and receiving agent, the Investigators at the Lead Organization and the Participating Organization(s) must obtain written approval to conduct the study from the appropriate IRB. Should changes to the study become necessary, protocol amendments will be submitted to the DCP PIO according to DCP Amendment Guidelines. The DCP-approved amended protocol must be approved by the IRB prior to implementation

14.4 Informed Consent

All potential study participants will be given a copy of the IRB-approved Informed Consent to review. The investigator will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the Informed Consent document. The study agent(s) will not be released to a participant who has not signed the Informed Consent document. Participants who refuse to participate or who withdraw from the study will be treated without prejudice.

Participants must be provided the option to allow the use of blood samples, other body fluids, and tissues obtained during testing, operative procedures, or other standard medical practices for further research purposes. If applicable, statement of this option may be included within the informed consent document or may be provided as an addendum to the consent. A Model Consent Form for Use of Tissue for Research is available through a link in the DCP website.

Prior to study initiation, the informed consent document must be reviewed and approved by NCI, DCP, the Consortium Lead Organization, and the IRB at each Organization at which the protocol will be implemented. Any subsequent changes to the informed consent must be approved by NCI, DCP, the Consortium Lead Organization's IRB, and then submitted to each organization's IRB for approval prior to initiation.

14.5 Submission of Regulatory Documents

All regulatory documents are collected by the Consortia Lead Organization and reviewed for completeness and accuracy. Once the Consortia Lead Organization has received complete and accurate documents from a participating organization, the Consortium Lead Organization will forward the regulatory documents to the DCP Regulatory Contractor:

Paper Document/CD-ROM Submissions:
Regulatory Affairs Department
CCS Associates
2001 Gateway Place, Suite 350 West
San Jose, CA 95110

Phone: 650-691-4400
Fax: 650-691-4410

E-mail Submissions:
regulatory@ccsainc.com

Regulatory documents that do not require an original signature may be sent electronically to the Consortium Lead Organization for review, which will then be electronically forwarded to the DCP Regulatory Contractor.

14.6 Other

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

15. FINANCING, EXPENSES, AND/OR INSURANCE

No expenses will be incurred by the study participant and/or their insurance carrier. This does not include any injuries or illnesses the participant may have related to their participation on the study. In the event of an injury or illness, the study participant and/or their insurance carrier will be responsible for all expenses related to the injury or illness. Participants may be provided remuneration for their participation in the study, at the discretion of the local Institutional Review Board.

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NCI, DCP Consent Form Template for Consortia Cancer Chemoprevention Trials

NOTES FOR LOCAL INVESTIGATORS*:

The goal of the informed consent process is to provide people with sufficient information for making informed choices about participating in research. The consent form provides a summary of the study, of the individual's rights as a study participant, and documents their willingness to participate. The consent form is, however, only one piece of an ongoing exchange of information between the investigator and study participant. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/

Please feel free to insert any language required by your IRB/REB. Please feel free to insert the language from this template consent form into a template required by your IRB/REB.

A blank line, "_____", indicates that the local investigator should provide the appropriate information before submitting to the IRB.

Prior to submission to your local IRB/REB, please remove all blue instructional text and submit your draft consent form to the CPN Operations Office for review, cancerpreventionnetwork@mayo.edu.

These notes for investigators are instructional and must be removed prior to submission to the IRB..

Study Title for Study Participants: Liver cancer prevention with erlotinib

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Pilot study of EGFR inhibition with erlotinib in cirrhosis to inhibit fibrogenesis and prevent hepatocellular carcinoma

Surgical Cohort

What is the usual approach to my fibrosis or cirrhosis of the liver?

The usual approach to fibrosis and cirrhosis depends upon the cause of your fibrosis or cirrhosis. The first step is to determine the cause or causes of the fibrosis or cirrhosis and discuss the dietary, lifestyle, and other issues that impact how well your liver works. Your

doctor may recommend a specific intervention to prevent worsening of your fibrosis or cirrhosis.

What are my other choices if I do not take part in this study?

You are being asked to take part in this study because you have fibrosis or cirrhosis of the liver and are scheduled for surgery to remove part of your liver.

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have surgery to remove part of your liver without taking part in this study,
- you may work with your health care provider to determine the causes of your fibrosis or cirrhosis and discuss the dietary, lifestyle, and other issues that may impact how well your liver works.
- you may choose to take part in a different study, if one is available,
- or you may choose to do nothing.

Why is this study being done?

The purpose of this study is to test the safety of erlotinib (Tarceva®) at different doses to find out what effects, if any, it has on people and their risk of liver cancer. Specifically, the investigators want to find the lowest dose that is safe and has an effect on the liver. There will be up to 65 people taking part in this study.

Erlotinib (Tarceva®) is a cancer medication pill that interferes with the growth and spread of cancer cells in the body in some types of cancer. Erlotinib (Tarceva®) is approved by the Food and Drug Administration (FDA) for the treatment of some cancers. It is not approved for the prevention or treatment of cirrhosis or cancer of the liver and is considered investigational (not FDA approved) as used in this study

What are the study groups?

Different doses of the study drug erlotinib (Tarceva®) will be given to several study participants. The first group of participants will receive 75 mg/day, which is lower than the dose usually prescribed for treatment for cancer. If the drug has an effect, a lower dose will be given to the next group of participants. If the drug does not have an effect, a slightly higher dose will be given. The study will be stopped when the investigators find the lowest possible dose that has an effect on the liver without worrisome side effects.

How long will I be in this study?

You will take the study medication once every day for approximately 7 days. The last dose will be taken the morning of your surgery. If your surgery is postponed for up to 7 more days, you will continue to take the study drug and remain on the study. Be sure to inform the study team

if this happens. If you do not finish the study, your doctor will continue to watch you for side effects and follow your condition until the time of your surgery.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your condition. However, there are some extra tests and procedures that you will need to have if you take part in this study.

Before you begin the study:

You will be asked to sign this consent form. You will then be pre-registered to the study and assigned a unique Participant Identification Number.

You will then need to have the following extra tests

- Physical exam and a review of your past medical history
- Discussion of any symptoms you are currently experiencing
- Discussion of any medications that you are taking (prescription drugs, over-the-counter medications, and dietary supplements)
- Pregnancy test, if you are female and able to become pregnant
- Blood tests to check your current liver function and for comparison with blood tests taken just before surgery (about 4 tablespoons of blood)
- Needle biopsy of the liver (4 pieces, each smaller than a pencil eraser)

During the needle biopsy of the liver, a small sample of your liver will be removed. This sample is required in order for you to take part in this study because the research on the sample is an important part of the study. Your doctor will determine which of the two following methods will be used to collect the sample:

1) A needle may be inserted through your skin into your liver or;
2) A needle may be inserted through a narrow flexible plastic tube that has been inserted into the large vein in your liver (hepatic vein) through a vein in your neck (jugular vein).

The procedure will be very similar to the procedure done to confirm your diagnosis of cirrhosis. A numbing drug will be used to control pain.

If the tests and procedures show that you can take part in the study, and you choose to, the date of your surgery will be confirmed. You will be registered to the study and assigned to one of the study drug dose level groups. You will be given a supply of the study drug and a diary to keep track of the pills you take and any symptoms you experience.

During the study, beginning on the 6th day prior to your surgery, you will take 1-6 pills of erlotinib at approximately the same time every day. The number of pills will depend upon the

dose level group to which you are assigned. You will take the pills every morning on an empty stomach. A member of the study team will call, text, or email you daily to remind you to take your study drug and to see how you are doing.

Prior to your surgery, you will have repeat blood tests for comparison with the tests you had prior to taking the study drug (about 4 tablespoons of blood). You will be asked about any side effects or symptoms. You will be asked about any other medications you are taking.

On the day of your surgery, you will take your last dose of study drug. After your surgery, a small piece of the liver tissue that was removed will be sent to the investigators for comparison with the liver biopsy specimen that was removed at the beginning of the study. This piece of liver tissue will be about the size of a sugar cube.

What possible risks can I expect from taking part in this study?

The drug used in this study may affect how different parts of your body work, such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health. There is also a risk that you could have side effects.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drug to try to reduce side effects.

The tables below show the most common side effects that we know about erlotinib, some of which may be serious. These known risks are for the standard dose of erlotinib. There might be other side effects that we do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of erlotinib:

COMMON, SOME MAY BE SERIOUS In 100 people receiving erlotinib, more than 20 people may have:
• Red or bumpy skin which may itch (rash) • Loose stool (diarrhea), which could lead to dehydration • Loss of appetite, not feeling hungry (anorexia) • Feeling sick to your stomach (nausea) • Throwing up (vomiting), which could lead to dehydration • Feeling tired (fatigue) • Infection • Shortness of breath or difficulty breathing (dyspnea) • Cough

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving erlotinib, from 4 to 20 may have:
• Sores in the mouth • Itching sensation (pruritus) • Acne • Dry skin (xerosis) • Weight loss • Irritation (redness, swelling, warmth, and pain) or infection of the skin around fingernails and toenails • Eye infection/pink eye • Dry, red, irritated eyes • Stomach pain or pain in the abdomen/belly

RARE, SOME MAY BE SERIOUS In 100 people receiving erlotinib, 3 or fewer may have:
Although very rare, some of the side effects listed below can cause death. • Changes in liver function tests which may indicate liver damage, this may be life threatening • Decreased kidney function. Kidney failure may require dialysis and could be life-threatening. • Inflammation of the lungs, scarring of the lungs, or upper respiratory infection (pneumonitis), which could be life-threatening. • Erosion of the lining of the stomach or intestines which can result in pain, bleeding (ulceration) or a hole in the intestinal lining (perforation) which can be life-threatening. This is more common in people who take some types of drugs (NSAIDS, corticosteroids, chemotherapy). Talk to your study doctor about drugs to avoid. • Severe blistering or peeling of skin (including hands and feet) which can be life-threatening • Damage or inflammation to the front of the eye (keratitis), which may lead to changes in vision • Hole or sore on the outer layer of the eye (cornea) caused by severe inflammation • Increased bleeding (Internal bleeding, nose bleed). More common in people who take blood thinning drugs. • Increased body hair growth, hair loss, eyelash/eyebrow changes, or brittle/loose fingernails or toenails. • In people with cancer of the pancreas who took combined treatment of erlotinib plus gemcitabine: heart attack, stroke, decreased red blood cells (anemia) which may cause tiredness, or may require blood transfusion and decreased platelets which may cause easy bleeding, or longer bleeding.

POSSIBLE, SOME MAY BE SERIOUS The frequency of some individual side effects has not yet been determined:
• Shoulder pain • Change in urine color • Depression • Indigestion, heartburn • Gas in the belly, burping, passing gas • Irritability (easily annoyed or made angry) • Swelling of the face, hands, feet, or ankles • Runny nose • Dizziness • Headache • Blood clot which may cause swelling, pain, shortness of breath • Death or injury to unborn baby

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The erlotinib used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

Risks of the liver biopsy include:

- Bleeding
- Soreness
- Infection at the site of the needle insertion through your skin or a vein in your neck and into your liver, which happens rarely.
- Low blood pressure that may cause lightheadedness or feeling faint
- A tear or hole in other internal organs that may require surgery
- An abnormal heartbeat, which happens rarely

Bleeding, infection, and other complications of the procedure are potentially life-threatening, and hospitalization might be required.

Risks of the blood draw: Bruising, soreness, or rarely, infection may occur as a result of the needle sticks to obtain blood from your vein.

Foods, medications, and activities that should be avoided during the study: There are a few foods, medications, and activities that may have an impact on the effectiveness of the study drug.

- While participating in the study, you should avoid grapefruit-containing products such as grapefruits, grapefruit juice, and any sodas that contain grapefruit juice (Fresca® and Squirt®).
- While participating in the study, you should not smoke or use any tobacco products.
- While participating in the study, you must be sure to inform the study team of any new medications, including over-the-counter medications, prescription drugs, and dietary supplements.

What possible benefits can I expect from taking part in this study?

Participating in this study is unlikely to help your condition. This study may help us learn things that could help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about any new information or changes in the study that could affect your health or your willingness to continue in the study

The study doctor may take you out of the study:

- If your health changes.
- If the study is no longer in your best interest.
- If new information becomes available.
- If you do not follow the study rules.
- If the study is stopped early for any reason by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number)*. *(Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

The erlotinib will be supplied at no charge while you take part in this study. The cost of study-specific biopsies and exams, tests, and any other procedures will be paid for by the study.

Some costs associated with your care may be considered standard of care, and will be billed to you or your insurance company. You will have to pay for any costs (including deductibles and co-payments) not covered by your health insurer. This includes the cost of your actual surgery and standard pre-surgical evaluations.

Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

What happens if I am injured or hurt because I took part in this study?

If you feel you have been injured or hurt as a result of taking part in the study, it is important that you tell the study doctor immediately. You will get medical treatment if you are injured or hurt as a result of taking part in this study.

Care for such research-related injuries will be billed in the ordinary manner, to you or your insurance. Treatment costs for research-related injuries not covered by your insurance will be paid by <*institution*>.

Note to participating organizations: *After consultation with DCP, the Mayo IRB, and Mayo Legal Contracts Administration, it was determined that CPN studies are to be considered non-therapeutic and participants should not be held liable for covering expenses related to injuries caused by participation in a clinical trial. There is no mechanism by which DCP can provide funding for treatment for study-related injuries, and individual participants should not be required to pay for such treatment. Please check with your local IRBs and other entities to determine the best language to use. The language in the paragraph above was approved by the Mayo Clinic IRB.*

Will I be paid for participating in this study?

You will not be paid for taking part. However, you may receive some funds to defray some of the cost of participating (e.g., parking, child care). If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

Note to participating organizations: You may provide whatever payments to the participants are allowed by your Institutional Review Board. Payments to each participant may not exceed a total of$270.00. You are allowed to break this into smaller payments for each visit and, if appropriate, provide that detail in this section.

Who will see my medical information?

Your privacy is very important to us and we will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, we will do our best to make sure that any information that is released will not be able to identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private. Some of these organizations are:

- The National Cancer Institute (NCI) and other government agencies, such as the Food and Drug Administration (FDA), involved in keeping research safe for people,
- Regulatory agencies within and outside the United States,
- The Institutional Review Board, which is a group of people who review the research with the goal of keeping the research safe for people,
- The National Cancer Institute will obtain information for this clinical trial under data collection authority Title 42 U.S.C. 285.

Where can I get more information?

You may visit the NCI website at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get

the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact your study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

This section is about optional studies you can choose to take part in.

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records, and you or your study doctor may not know the results. You will not be billed for these optional studies.

You can still take part in the main study even if you say "no" to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your biopsies and blood that are left over after the study analyses are complete. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

What is involved?

If you agree to allow the use of your leftover blood and tissue, your samples and some related information may be stored in the Cancer Prevention Network Biobank at the Mayo Clinic, along with samples and information from other people who take part. The samples will be kept until they are used up.

Qualified researchers can submit a request to use the materials stored in the Biobank. A research committee at the clinical trials organization and the National Cancer Institute will review each request. There will also be an ethics review to ensure that the request is necessary

and proper. Researchers will not be given your name or any other information that could directly identify you.

Neither you nor your study doctor will be notified if/when research is conducted using your samples. Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

What are the possible risks?

There is a risk that someone could get access to the personal information in your medical records or other information we have stored about you.

There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

There are laws against the misuse of genetic information, but they may not give full protection.

New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

How will information about me be kept private?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1. When your sample(s) is sent to the researchers, no information identifying you (such as your name or social security number) will be sent.
2. Samples will be identified using a unique code only. The list that links the unique code to your name will be kept separate from your sample and health information.
3. Any Cancer Prevention Network staff with access to the list must sign an agreement to keep your identity confidential.
4. Researchers to whom the Cancer Prevention Network sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
5. Information that identifies you will not be given to anyone unless required by law.
6. If the research results are published, your name and other personal information will not be used.

What are the possible benefits?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

What if I have more questions or change my mind?

If you decide you no longer want your samples to be used, you can call Contact your study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers will not be returned.

Making your choice

Circle your choice of "yes" or "no" for each of the following studies.

1. My blood and tissue may be kept for use in future research to learn about, prevent, treat, or cure cancer.

Yes No Initials_____

2. My blood and tissue may be kept for use in future research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No Initials_____

3. My blood and/or tissue may be sent to researchers at outside institutions.

Yes No Initials_____

4. Someone may contact me in the future to ask permission to use my specimens in new research not included in this consent.

Yes No Initials_____

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled "YES."

Participant's signature _____

Date of signature_____

Signature of person(s) conducting the informed consent discussion _____

Date of signature_____

Study Calendar – Optional Attachment to the Consent Form

Time Point	Visits and Tests
Baseline	• Sign consent form • Medical history, review of current symptoms and illnesses • Review of allergies and any medications you are taking • Physical exam • Vital signs (height, weight, blood pressure, temperature) • Blood tests to check your current condition and have a baseline that can be used for comparison with blood tests at the end of the study. Approximately 2 tablespoons of blood will be drawn for these tests. • Collection of blood for research (an additional 2 tablespoons). • Pregnancy test, if applicable
Just before beginning the study	• Biopsy of your liver
First day of the study	• Pregnancy test, if applicable, and if it has been more than 7 days since the first test • Take your first dose of study drug • Receive a medication diary to record taking study drug and any other symptoms you may experience
Days 1-7	• Take a dose of study drug every day. • Record taking the drug and any symptoms you may experience • A member of the study team will call you every day during the study to see how you're doing and review the schedule for the last two days of the study.
Before surgery	• Physical exam • Review symptoms and current medications • Review and collect medication diary and any leftover study drug (with the exception of the very last pill) • Remember to take your study drug according to the schedule • Complete a questionnaire
Day of surgery	• Take your last dose of study drug with a sip of water before the blood tests and surgery. • Blood tests for safety and comparison. Approximately 2 tablespoons of blood will be drawn for these tests. • Collection of blood for research (an additional 2 tablespoons).

NCI, DCP Consent Form Template for Consortia Cancer Chemoprevention Trials

NOTES FOR LOCAL INVESTIGATORS*:

The goal of the informed consent process is to provide people with sufficient information for making informed choices about participating in research. The consent form provides a summary of the study, of the individual's rights as a study participant, and documents their willingness to participate. The consent form is, however, only one piece of an ongoing exchange of information between the investigator and study participant. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/

Please feel free to insert any language required by your IRB/REB. Please feel free to insert the language from this template consent form into a template required by your IRB/REB.

A blank line, "_____", indicates that the local investigator should provide the appropriate information before submitting to the IRB.

Prior to submission to your local IRB/REB, please remove all blue instructional text and submit your draft consent form to the CPN Operations Office for review, cancerpreventionnetwork@mayo.edu.

These notes for investigators are instructional and must be removed prior to submission to the IRB..

Study Title for Study Participants: Liver cancer prevention with erlotinib

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Pilot study of EGFR inhibition with erlotinib in cirrhosis to inhibit fibrogenesis and prevent hepatocellular carcinoma

Non-Surgical Cohort

What is the usual approach to my fibrosis or cirrhosis of the liver?

The usual approach to fibrosis and cirrhosis depends upon the cause of your fibrosis or cirrhosis. The first step is to determine the cause or causes of the fibrosis or cirrhosis and discuss the dietary, lifestyle, and other issues that impact how well your liver works. Your doctor may recommend a specific intervention to prevent worsening of your fibrosis or cirrhosis.

What are my other choices if I do not take part in this study?

You are being asked to take part in this study because you have fibrosis or cirrhosis of the liver and have had a liver biopsy in the past three months.

If you decide not to take part in this study, you have other choices. For example:

- You may work with your health care provider to determine the causes of your fibrosis or cirrhosis and discuss the dietary, lifestyle, and other issues that may impact how well your liver works,
- you may choose to take part in a different study, if one is available,
- or you may choose to do nothing.

Why is this study being done?

The purpose of this study is to test the safety of erlotinib (Tarceva®) at different doses to find out what effects, if any, it has on people and their risk of liver cancer. Specifically, the investigators want to find the lowest dose that is safe and has an effect on the liver. There will be up to 65 people taking part in this study.

Erlotinib (Tarceva®) is a cancer medication pill that interferes with the growth and spread of cancer cells in the body in some types of cancer. Erlotinib (Tarceva®) is approved by the Food and Drug Administration (FDA) for the treatment of some cancers. It is not approved for the prevention or treatment of cirrhosis or cancer of the liver and is considered investigational (not FDA approved) as used in this study

What are the study groups?

Different doses of the study drug erlotinib (Tarceva®) will be given to several study participants. The first group of participants will receive 75 mg/day, which is lower than the dose usually prescribed for treatment for cancer. If the drug has an effect, a lower dose will be given to the next group of participants. If the drug does not have an effect, a slightly higher dose will be given. The study will be stopped when the investigators find the lowest possible dose that has an effect on the liver without worrisome side effects.

How long will I be in this study?

You will take the study medication once every day for approximately 7 days. The last dose will be taken the morning of your liver biopsy. If your biopsy is postponed for up to 7 more days, you will continue to take the study drug and remain on the study. Be sure to inform the study team if this happens. If you do not finish the study, your doctor will continue to watch you for side effects and follow your condition until the time of your surgery.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your condition. However, there are some extra tests and procedures that you will need to have if you take part in this study.

Before you begin the study:

You will be asked to sign this consent form. You will then be pre-registered to the study and assigned a unique Participant Identification Number.

You will be asked for your permission to obtain a sample of the tissue removed during your liver biopsy. This sample will be sent to the investigators at the Mayo Clinic to see if it tests positive for phosphorylated Epidermal Growth Factor Receptor (phospho-EGFR) which is a protein that can be found on the surface of cells and plays a role in cell division.

If your liver biopsy tissue is positive for phospho-EGFR, and you are still willing to participate in the study, you will need to have the following extra tests

- Physical exam and a review of your past medical history
- Discussion of any symptoms you are currently experiencing
- Discussion of any medications that you are taking (prescription drugs, over-the-counter medications, and dietary supplements)
- Pregnancy test, if you are female and able to become pregnant
- Blood tests to check your current liver function and for comparison with blood tests taken just before surgery (about 4 tablespoons of blood)

You will also be scheduled for another biopsy of the liver so that tissue can be obtained for comparison to tissue from your previous biopsy.

During the study, beginning on the 6^{th} day prior to your biopsy, you will take 1-6 pills of erlotinib at approximately the same time every day. The number of pills will depend upon the dose level group to which you are assigned. You will take the pills every morning on an empty stomach. A member of the study team will call, text, or email you daily to remind you to take your study drug and to see how you are doing.

Prior to your biopsy, you will have repeat blood tests for comparison with the tests you had prior to taking the study drug (about 4 tablespoons of blood). You will be asked about any side effects or symptoms. You will be asked about any other medications you are taking.

On the day of your biopsy, you will take your last dose of study drug. The study team will also ask you about side effects and other medications you are taking. You will be asked to complete a brief questionnaire.

During the needle biopsy of the liver, a small sample of your liver will be removed. This sample is required in order for you to take part in this study because the research on the sample is an important part of the study. Your doctor will determine which of the two following methods will be used to collect the sample:

1) A needle may be inserted through your skin into your liver or;
2) A needle may be inserted through a narrow flexible plastic tube that has been inserted into the large vein in your liver (hepatic vein) through a vein in your neck (jugular vein).

The procedure will be very similar to the procedure done to confirm your diagnosis of cirrhosis. A numbing drug will be used to control pain.

After your biopsy, a small piece of the liver tissue that was removed will be sent to the investigators for comparison with the liver biopsy specimen that was obtained at the beginning of the study. This piece of liver tissue will be about the size of a sugar cube.

What possible risks can I expect from taking part in this study?

The drug used in this study may affect how different parts of your body work, such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health. There is also a risk that you could have side effects.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drug to try to reduce side effects.

The tables below show the most common side effects that we know about erlotinib, some of which may be serious. These known risks are for the standard dose of erlotinib. There might be other side effects that we do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of erlotinib:

COMMON, SOME MAY BE SERIOUS In 100 people receiving erlotinib, more than 20 people may have:
• Red or bumpy skin which may itch (rash) • Loose stool (diarrhea), which could lead to dehydration • Loss of appetite, not feeling hungry (anorexia) • Feeling sick to your stomach (nausea) • Throwing up (vomiting), which could lead to dehydration • Feeling tired (fatigue) • Infection • Shortness of breath or difficulty breathing (dyspnea) • Cough

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving erlotinib, from 4 to 20 may have:
• Sores in the mouth • Itching sensation (pruritus) • Acne • Dry skin (xerosis) • Weight loss • Irritation (redness, swelling, warmth, and pain) or infection of the skin around fingernails and toenails • Eye infection/pink eye • Dry, red, irritated eyes • Stomach pain or pain in the abdomen/belly

RARE, SOME MAY BE SERIOUS In 100 people receiving erlotinib, 3 or fewer may have:
Although very rare, some of the side effects listed below can cause death. • Changes in liver function tests which may indicate liver damage, this may be life threatening • Decreased kidney function. Kidney failure may require dialysis and could be life-threatening. • Inflammation of the lungs, scarring of the lungs, or upper respiratory infection (pneumonitis), which could be life-threatening. • Erosion of the lining of the stomach or intestines which can result in pain, bleeding (ulceration) or a hole in the intestinal lining (perforation) which can be life-threatening. This is more common in people who take some types of drugs (NSAIDS, corticosteroids, chemotherapy). Talk to your study doctor about drugs to avoid. • Severe blistering or peeling of skin (including hands and feet) which can be life-threatening • Damage or inflammation to the front of the eye (keratitis), which may lead to changes in vision • Hole or sore on the outer layer of the eye (cornea) caused by severe inflammation • Increased bleeding (Internal bleeding, nose bleed). More common in people who take blood thinning drugs. • Increased body hair growth, hair loss, eyelash/eyebrow changes, or brittle/loose fingernails or toenails. •

POSSIBLE, SOME MAY BE SERIOUS The frequency of some individual side effects has not yet been determined:
• Shoulder pain • Change in urine color • Depression • Indigestion, heartburn • Gas in the belly, burping, passing gas • Irritability (easily annoyed or made angry) • Swelling of the face, hands, feet, or ankles • Runny nose • Dizziness • Headache • Blood clot which may cause swelling, pain, shortness of breath •

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The erlotinib used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

Risks of the liver biopsy include:

- Bleeding
- Soreness
- Infection at the site of the needle insertion through your skin or your neck vein and into your liver, which happens rarely.
- Low blood pressure that may cause lightheadedness or feeling faint
- A tear or hole in other internal organs that may require surgery
- An abnormal heartbeat, which happens rarely

Bleeding, infection, and other complications of the procedure are potentially life-threatening, and hospitalization might be required.

Risks of the blood draw: Bruising, soreness, or rarely, infection may occur as a result of the needle sticks to obtain blood from your vein.

Foods, medications, and activities that should be avoided during the study: There are a few foods, medications, and activities that may have an impact on the effectiveness of the study drug.

- While participating in the study, you should avoid grapefruit-containing products such as grapefruits, grapefruit juice, and any sodas that contain grapefruit juice (Fresca® and Squirt®).
- While participating in the study, you should not smoke or use any tobacco products.
- While participating in the study, you must be sure to inform the study team of any new medications, including over-the-counter medications, prescription drugs, and dietary supplements.

What possible benefits can I expect from taking part in this study?

Participating in this study is unlikely to help your condition. This study may help us learn things that could help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about any new information or changes in the study that could affect your health or your willingness to continue in the study

The study doctor may take you out of the study:

- If your health changes.
- If the study is no longer in your best interest.
- If new information becomes available.
- If you do not follow the study rules.
- If the study is stopped early for any reason by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number)*. *(Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

The erlotinib will be supplied at no charge while you take part in this study. The cost of study-specific biopsies and exams, tests, and any other procedures will be paid for by the study.

Some costs associated with your care may be considered standard of care, and will be billed to you or your insurance company. You will have to pay for any costs (including deductibles and co-payments) not covered by your health insurer. This includes the cost of your actual surgery and standard pre-surgical evaluations.

Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

What happens if I am injured or hurt because I took part in this study?

If you feel you have been injured or hurt as a result of taking part in the study, it is important that you tell the study doctor immediately. You will get medical treatment if you are injured or hurt as a result of taking part in this study.

Care for such research-related injuries will be billed in the ordinary manner, to you or your insurance. Treatment costs for research-related injuries not covered by your insurance will be paid by <*institution*>.

Note to participating organizations: *After consultation with DCP, the Mayo IRB, and Mayo Legal Contracts Administration, it was determined that CPN studies are to be considered non-therapeutic and participants should not be held liable for covering expenses related to injuries*

caused by participation in a clinical trial. There is no mechanism by which DCP can provide funding for treatment for study-related injuries, and individual participants should not be required to pay for such treatment. Please check with your local IRBs and other entities to determine the best language to use. The language in the paragraph above was approved by the Mayo Clinic IRB.

Will I be paid for participating in this study?

You will not be paid for taking part. However, you may receive some funds to defray some of the cost of participating (e.g., parking, child care). If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

Note to participating organizations: You may provide whatever payments to the participants are allowed by your Institutional Review Board. Payments to each participant may not exceed a total of$270.00. You are allowed to break this into smaller payments for each visit and, if appropriate, provide that detail in this section.

Who will see my medical information?

Your privacy is very important to us and we will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, we will do our best to make sure that any information that is released will not be able to identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private. Some of these organizations are:

- The National Cancer Institute (NCI) and other government agencies, such as the Food and Drug Administration (FDA), involved in keeping research safe for people,
- Regulatory agencies within and outside the United States,
- The Institutional Review Board, which is a group of people who review the research with the goal of keeping the research safe for people,
- The National Cancer Institute will obtain information for this clinical trial under data collection authority Title 42 U.S.C. 285.

Where can I get more information?

You may visit the NCI website at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required

by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact your study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number)*.

This section is about optional studies you can choose to take part in.

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records, and you or your study doctor may not know the results. You will not be billed for these optional studies.

You can still take part in the main study even if you say "no" to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your biopsies and blood that are left over after the study analyses are complete. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

What is involved?

If you agree to allow the use of your leftover blood and tissue, your samples and some related information may be stored in the Cancer Prevention Network Biobank at the Mayo Clinic, along with samples and information from other people who take part. The samples will be kept until they are used up.

Qualified researchers can submit a request to use the materials stored in the Biobank. A research committee at the clinical trials organization and the National Cancer Institute will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.

Neither you nor your study doctor will be notified if/when research is conducted using your samples. Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

What are the possible risks?

There is a risk that someone could get access to the personal information in your medical records or other information we have stored about you.

There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

There are laws against the misuse of genetic information, but they may not give full protection.

New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

How will information about me be kept private?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1. When your sample(s) is sent to the researchers, no information identifying you (such as your name or social security number) will be sent.
2. Samples will be identified using a unique code only. The list that links the unique code to your name will be kept separate from your sample and health information.
3. Any Cancer Prevention Network staff with access to the list must sign an agreement to keep your identity confidential.
4. Researchers to whom the Cancer Prevention Network sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
5. Information that identifies you will not be given to anyone unless required by law.
6. If the research results are published, your name and other personal information will not be used.

What are the possible benefits?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

What if I have more questions or change my mind?

If you decide you no longer want your samples to be used, you can call Contact your study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers will not be returned.

Making your choice

Circle your choice of "yes" or "no" for each of the following studies.

1. My blood and tissue may be kept for use in future research to learn about, prevent, treat, or cure cancer.

Yes No Initials_____

2. My blood and tissue may be kept for use in future research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No Initials_____

3. My blood and/or tissue may be sent to researchers at outside institutions.

Yes No Initials_____

4. Someone may contact me in the future to ask permission to use my specimens in new research not included in this consent.

Yes No Initials_____

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled "YES."

Participant's signature _____

Date of signature_____

Signature of person(s) conducting the informed consent discussion _____

Date of signature_____

Study Calendar – Optional Attachment to the Consent Form

Time Point	Visits and Tests
Informed consent	• Sign consent form • Provide permission to obtain specimens from your previous liver biopsy
Screening	• Medical history, review of current symptoms and illnesses • Review of allergies and any medications you are taking • Physical exam • Vital signs (height, weight, blood pressure, temperature) • Blood tests to check your current condition and have a baseline that can be used for comparison with blood tests at the end of the study. Approximately 2 tablespoons of blood will be drawn for these tests. • Collection of blood for research (an additional 2 tablespoons). • Pregnancy test, if applicable
First day of the study	• Pregnancy test, if applicable, and if it has been more than 7 days since the first test • Take your first dose of study drug • Receive a medication diary to record taking study drug and any other symptoms you may experience
Days 1-7	• Take a dose of study drug every day. • Record taking the drug and any symptoms you may experience • A member of the study team will call you every day during the study to see how you're doing and review the schedule for the last two days of the study.
Before biopsy	• Physical exam • Review symptoms and current medications • Review and collect medication diary and any leftover study drug (with the exception of the very last pill) • Remember to take your study drug according to the schedule • Complete a questionnaire
Day of biopsy	• Take your last dose of study drug with a sip of water before the blood tests and biopsy. • Blood tests for safety and comparison. Approximately 2 tablespoons of blood will be drawn for these tests. • Collection of blood for research (an additional 2 tablespoons).

Appendix A. Performance Status Criteria

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

Appendix B. Was It Worth It (WIWI) Questionnaire

Visit type (Time point):* ☐ Day prior to surgery or biopsy (or early termination)

Participating in a clinical trial / research study is a personal choice and an individual experience. We would like to get your feedback on your experience in this research study. Please respond to the following questions as indicated.

Directions: Please answer each question by circling Y (for yes), N (for no), or U (for uncertain).

Was it worthwhile for you to participate in this research study?	Y	N	U
If you had to do it over, would you participate in this research study again?	Y	N	U
Would you recommend participating in this research study to others?	Y	N	U

Directions: Circle one response

Overall, did your quality of life change by participating in this research study?

It improved It stayed the same It got worse

Overall, how was your experience of participating in this research study?

Better than I expected The same as I expected Worse than I expected

If there was one thing **that could have been done to improve your experience in this research study, what would it be?**

_____

_____

_____

Would you like to talk to someone about your concerns (circle one response)? Yes No

_____ _____

Signature Date

Appendix C. Recruitment, Retention, and Adherence Plan Template

MAY2013-02-02 Pilot Study of EGFR Inhibition with Erlotinib in Cirrhosis to Inhibit Fibrogenesis and Prevent Hepatocellular Carcinoma

Instructions: *NCI, DCP requires a site and study-specific recruitment, retention, and adherence (RRA) plan for each organization participating in a cancer chemoprevention study. Each participating organization should tailor the study RRA plan template to meet the needs at their local site. The RRA plan outline below is intended as a tool to assist site investigators and recruitment coordinators in the RRA planning process.*

Black/Bold font indicates required components of the plan

Instructions for specific information Participating Organizations should insert into each section are in blue italics. These should be deleted when the site-specific RRA plan is complete. When complete, please submit your RRA Plan to the CPN Operations Office for review.

I. Pre-initiation phase (Developing the Recruitment, Retention, and Adherence Plan) prior to the Study Initiation Meeting.

A. Determine staff assignments *(It may be helpful to specify by job title the individual(s) on the site team who will fill each of the roles described below)*

1. Identify the RRA coordinator for the study. This person will have primary responsibility for coordinating all aspects of recruitment for this study, including but not limited to, reviewing databases, medical records, and previous studies' participants lists for potentially eligible study participants of both genders, all races, and all ethnic groups; contacting these individuals to assess interest and initial eligibility (in whatever manner is most appropriate for the study and the institution); setting up appointments for screening and informed consent (including checking investigators' schedules for appointment and procedures); and maintaining contact with study participants throughout their participation to insure compliance with the protocol.
2. Identify alternate recruiters and back up personnel will be assigned to assist as needed.
3. Outline the role of the site PI and site co-investigators (all listed on the study-specific FDA form 1572) will:
    a. Assist in the initial assessment of eligibility
    b. Meet with the RRA coordinator regularly and be accessible to the RRA coordinator to monitor recruitment and accrual activity as well as progress of individuals on study
    c. Give appropriate decision-making authority to the RRA Coordinator
    d. Monitor recruitment
    e. Meet with staff regularly. Provide information and training to other departmental personnel as needed to maintain an appropriate level of recruitment and consistent implementation of the protocol.

B. Review protocol design and its impact on recruitment

1. Evaluate feasibility of sample size:
    a. Availability of target population considering demographics
    b. Availability of target population considering eligibility criteria

   c. Possible effects of placebo control arm
2. Determine possible effects of participant access to FDA-approved studies
   a. Possible effects of potential toxicity
   b. Possible effects of complicated entry criteria and burdensome protocol procedures
3. Calculate availability of eligible participants based on:
   a. Consultation with potential participants
   b. Review of patient lists within each practice. If appropriate and necessary, contact referring physicians for permission to contact their patients.
   c. Review of the literature
   d. Calculate the number of eligible enrolled participants versus number of eligible participants who chose not to enroll per site
   e. Estimate accrual rate (# of participants per month). *Please note that the CPN Operations Office will request this information prior to study activation. This target will be evaluated on a monthly basis and will work with each PO to review and, if needed, revise the RRA plan to address this.*
4. After a pre-determined period of time,* (if timeframe for achieving overall recruitment goal is unrealistic), considerations for protocol modifications include the following:
   a. Broadening eligibility criteria (e.g. time frames for completion of tests and procedures, lab values)
   b. Simplifying protocol
   c. Decreasing sample size
   d. Extending recruitment period

C. Outline a plan to Identify and Contact Known and Potential Referral Sources

1. Survey potential referral doctors, obtain letter of commitment if possible. Cultivate working relationship with non-oncology specialists who provide care related to the study target organ (e.g. Gastroenterologists, Internists, etc.).
2. Non-physician referrals - Enlist endorsement and cooperation to promote enrollment:
   a. Community centers e.g. Jewish Community Centers (JCC)
   b. Retirement communities
   c. Senior centers
   d. YMCAs, public libraries, etc.
   e. Health clubs
   f. Churches
   g. Local corporations
   h. Alliances with disease specific organizations, such as patient advocacy groups, support groups, and charitable organizations
3. Keep referring physicians updated and engaged using tools such as:
   a. Letters to referring physicians
   b. Quick fact sheets and cards
   c. Study information posted in physician work areas

D. Determine and Document Metrics for evaluation of RRA Performance

1. Estimated total accrual per PO will be ____ per site, with an average of ___ participants registered per site per month. *These blanks should be completed based on B.3.e above with assistance from the CPN Operations Office.*
2. Keep site study teams updated and engaged.

   a. Recruitment strategies will be discussed at all the study coordinator teleconferences to discuss general effectiveness as well as other approaches. Modified or alternative plans will be implemented if recruitment or retention is lagging.
   b. Weekly accrual reports will be generated by the CPN Statistical Programmer Analyst and sent to all appropriate study personnel. These will be summarized and posted on the CPN website.
   c. Each site will submit monthly screening and recruitment activity reports, which will be summarized and forwarded to DCP study personnel. These will be reviewed at least monthly by the CPN Operations Office and discussed at all study coordinator teleconferences.
   d. CPN Operations Office will keep open communication with study sites, sending out a monthly memo, scheduled study coordinator and PI teleconferences, and discussing logistical problems. The CPN Operations Office will be available to assist with resolution of any identified problems.
3. Calculate the cost of enrollment per participant.
4. Develop a plan to track participant screen failures and withdrawals, including reasons for both.
5. Consider surveying participants' opinions of the RRA strategies.
6. After initial activation of the study, overall accrual will be evaluated monthly. If by a predetermined period of time* after initial activation at a given site, participant accrual is lagging behind the target, the CPN Operations Office will have a teleconference with the site PI and team to discuss issues/obstacles. A timeframe, i.e. six months, will be determined during which the site team must implement its action plan. If recruitment activity is determined to be unsatisfactory at this point, the site will be asked to close to accrual.

**** The time points at which accrual milestones must be met will be determined collaboratively between the Study Chair, CPN Operations Office team, the DCP Medical Monitor, and each PO's recruitment coordinator.***

Participating Organizations: Please revise the section E below to describe your site's specific plans to train study team member and provide any pertinent study updates to them. The Study Coordinator Memo mentioned above will be sent to the lead Study Coordinator. Plans should be described to distribute the memo and/or any protocol-related material to all pertinent site study team members.

E. Outline Plan to Train Staff in Recruitment

1. Educate staff regarding recruitment and protocol specifics (after protocol is approved).
2. Develop and distribute protocol summary pocket cards or electronic equivalent.
3. Develop Frequently Asked Questions (FAQ) documents.
4. Train support staff and maintain documentation of all training.
   a. Hospitality and smooth clinic flow
   b. Procedural requirements, i.e. fasting.
   c. Procedures to follow when there are protocol violations.
5. Prepare a script to explain protocol to participants.
6. Resources provided by the CPN Operations Office
   a. Study coordinator and PI teleconference will be held throughout the study every 4-6 weeks or as needed.
   b. CPN Newsletter will be distributed twice yearly
   c. Recognition of high recruiters and sharing of their specific strategies

d. Draft recruitment, retention, and adherence materials that can be modified by each Participating Organization for review by local IRB prior to use at each Participating Organization. These may also include public services announcements, use of social media, such as Twitter, and videos to upload to YouTube®.
e. Buddy system among site study coordinators
f. Holiday cards with approved study-specific news for distribution to enrolled participants (after appropriate approvals are received)

Participating Organizations: Please add any additional information necessary to Section F below to adequately describe your site's plans for implementing appropriate informed consent process and creating a positive clinical trial experience for your participants.

F. Outline a Plan to Promote a Comfortable and Pleasant Clinic Environment/Experience in accordance with institutional policies and procedures. The following are recommended:

1. Supply driving directions to schedulers.
2. Coordinate well-organized clinic flow.
3. Assure user-friendly test scheduling, drug dispensing or immunization administration (as applicable), etc.
4. Negotiate (if possible, insist upon) flexible appointment times (i.e., more than one day per week).
5. Plan to allow ample time for participants with the clinical trial staff for the entire informed consent process.
6. Schedule periodic meetings between the clinic coordinator and the protocol staff.

Participating Organizations: Please describe in section G any participant compensation or remuneration, if applicable. Please also describe the time and/or funds that will be devoted to participant recruitment, retention, and adherence.

G. Outline the Budget:
The overall budget for this study will involve a standard amount for each participant accrued to the study. Partial payments will be made for participants who are determined to be screen failures. All payments will be made when all of the data (case report forms) up to the point of going off study are submitted. The site subcontracts do not specify how the per-patient reimbursement is to be allocated. The following should be considered at each site as appropriate to successful implementation of the study:

1. Staff time to implement recruitment and retention plan
2. Recruiter transportation to community outreach events
3. Participant compensation/remuneration
4. Recruitment and retention tools (See Section H)

H. Determine and outline site-specific recruitment and retention strategies based on evaluation of protocol, target population, clinic, and referral sources. Remember to adhere to local IRB requirements as to whether or not IRB approval is required for these strategies.

1. Regular contact with referral sources

2. General strategies
    a. Advertisements and public relations
    b. Newspaper
    c. TV and radio
    d. Internet, social networking sites such as Pinterest, Twitter, and Facebook
    e. Direct mailings
    f. Investigator interviews
    g. Patient education lectures
    h. Investigator or coordinator educational sessions to relevant community organizations
    i. FAQ documents
    j. Mass media and press releases
    k. Partner with other studies
    l. Identify Spokespersons
    m. Volunteers
3. **Describe recruitment strategies for special populations, with emphasis on plans to recruit individuals of both genders and all races and ethnic groups:**
    a. Perform cultural assessment of local communities
    b. Consider centralized minority coordinator
    c. Consider matched ethnicity recruitment coordinator
    d. Have translator available
    e. Minority community liaison
    f. Meet with minority community leaders
    g. Go to community meetings
    h. Establish relationships with churches
    i. Special needs participants
    j. Large print documents
    k. Arrange transportation
4. Partner with other studies (and study teams)
5. Identify spokespersons

Participating Organizations: Revise Section II (below) to describe your actual recruitment strategies. Describe specifically how you will identify potential participants, screen potential participants, and begin the informed consent process.

II. Active recruitment phase (Implementing the Recruitment Plan)

1. Implement strategies as determined during planning phase
2. Assess eligibility of individual potential participants
3. Consider non-compliance and retention potential
    a. Exclude participants unlikely to comply and stay on study – unless you can provide compensatory support and follow-up
    b. Known history of non-compliance
        i. Socially unstable
        ii. Expressed difficulty with, and numerous objections to, protocol requirements
        iii. Cavalier attitude toward protocol
        iv. Verbalized a minimization of cancer risk

v. Verbalized desire for "active immunization only"

c. Clarify each individual's objections to enrollment.
   i. Clarify misconceptions
   ii. Work to resolve manageable logistical problems
   iii. Consider multiple objections as red flag indicating possible retention/compliance problems
   iv. Involve participant's support system in decision-making

d. Continuously evaluate strategies as planned during pre-initiation phase.
   i. Monitor and document task completion in a timely way (regulatory requirements, regular meetings, and meeting minutes)
   ii. Document evaluation of strategies and outcomes as planned
      1. Track results of each strategy
      2. Maintain screening/enrollment log forms
      3. Calculate cost of enrollment per participant
      4. Survey participants' opinions: strengths and weaknesses of strategies
   iii. Rapidly implement modified or alternative plans if recruitment is lagging

Participating Organizations: Revise Section III below to describe the activities you will employ to maintain contact with the study participants while on study and insure compliance with events, procedures, and study medication. Please also describe any activities that you do to maintain a good relationship with them so that they might, if eligible, be willing to participate in future clinical trials. The activities listed are ideas and suggestions.

III. Retention and adherence phase – Be proactive

1. Maintain communication with referring physicians re: participant progress
2. Establish and maintain rapport among staff during follow-up
   a. Newsletters or other communication tools
   b. All-site teleconferences/web conferences
   c. Adequate staff compensation
   d. Staff recognition/awards
   e. Non protocol staff recognition, e.g. clinic and support staff
3. Establish and maintain rapport and communication with participants
   a. Identify and track red flags for possible attrition (but do not offer support that cannot be maintained):
      i. Adverse effects/events (review protocol carefully, be prepared to respond to AE reports, inform participants as to what can be expected)
      ii. Missed appointments
      iii. Frequent appointment time changes
      iv. Major personal or family events
      v. Health deterioration
      vi. Loss of support system
      vii. Do not promise support that cannot be maintained
   b. Adverse events
      i. Inform participants as to what to expect
      ii. Have a prepared AE management protocol/plan
   c. Maintain current contact info for each participant

d. Enlist support of participant's social network
    i. Transportation
    ii. Encouragement
    iii. Protocol compliance
e. Provide remuneration/compensation for expenses incurred as budget and local IRB regulations permit:
    i. Parking, meals, time lost from work, transportation, child care
f. Ensure pleasant clinic visits
    i. Limit waiting room time and provide refreshments, if possible
    ii. Coordinate assessments (e.g., blood work, etc.) with visits
    iii. Flexible scheduling
    iv. Toll-free numbers
    v. Ensure consistent staff contact person and access to PI
    vi. Establish and communicate schedule for contact with participant
    vii. Consider retention tools, such as calendars, newsletters, appointment cards, reminder cards and phone calls, certificates of appreciation, holiday cards
g. Ensure consistent staff contact person and access to PI
h. Establish schedule for contact with participant
i. Consider retention tools
    i. Calendars
    ii. Newsletter
    iii. Appointment reminders calls, cards, emails
    iv. Anniversary or holiday cards
    v. Certificates of appreciation
    vi. T-shirts, mugs, magnets (or IRB-other approved tools)
    vii. Support groups
j. Track participant withdrawals and reasons for withdrawal and communicate this information to the CPN Operations Office

Participating Organizations: Section IV describes the activities of the CLO. It should be left in your site's plan for informational purposes. Additionally, you are encouraged to describe any analysis or evaluation of recruitment that will occur at your site.

IV. Evaluation Phase

1. During the study

a. The CPN Operations Office team will continuously review study recruitment and adherence data from all tracking documents. These will be summarized and reported on a monthly basis.

b. The CPN Operations Office team will review the monthly reports and discuss possible revisions, protocol modifications, site closures, and other activities as needed.

c. All discussions, recommendations, conclusions, and/or lessons learned will be documented with the possibility of publication in mind.

d. Successful strategies will be shared with other POs during teleconferences and via the Study Coordinator Memo.

2. After the study

a. Historically it has been difficult to reach recruitment goals across all cancer prevention studies. In order to explore the obstacles sites are facing, the CLO will distribute a

short survey to all participating sites at the study completion. The survey will target: site issues, inclusion/exclusion issues, time issues, CPN support, education and training.

b. The CPN Operations Office team will apply knowledge gained to all future study recruitment efforts.

Appendix D. Medication Diary

Participant ID _____ **Study physician** _____

Instructions: This is a checklist for you to use to record taking your study drug. Please put a check mark beside each day as you take the study drug. Remember: Please take the drug 1 hour before or 2 hours after eating. Use the back side of this chart to record any side effects or symptoms you experience.

Date	Time study drug was taken	Fasting?	Date and Time of last meal	Any New Medications? Please list. Use the back of this page if needed.
Example: Day 0 Date: 9/6/2016	*5:30 am*	*√ Yes*	*9/5/2016 7:00 pm*	*Ibuprofen for headache, 2:00 p.m., okay by 3:00 p.m.*
☐ Day 1 Date _____				
☐ Day 2 Date _____				
☐ Day 3 Date _____				
☐ Day 4 Date _____				
☐ Day 5 Date _____				
☐ Day 6 Date _____				
☐ Day 7 Date _____				
☐ Day 8 Date _____				
☐ Day 9 Date _____				
☐ Day 10 Date _____				
☐ Day 12 Date _____				
☐ Day 13 Date _____				
☐ Day 14 Date _____				

Participant Signature _____ **Date** _____

Study Coordinator Signature _____ **Date** _____

Symptoms: Please list any side effects or symptoms you experience. If possible, note the date the symptoms started and the date they disappeared.

Appendix E. Schema Summary

Schema Describing Dose Level Assignment
MTD: Maximum Tolerated Dose
DLT: Dose Limiting Toxicity

Safety is defined as < 33% DLT.
Efficacy is defined as ≥ 40% demonstrate reduction in EGFR staining,

Enrollment will be in cohorts of 5 as described in Section 7.4.2. Accrual will be temporarily halted after each cohort of 5 to evaluate safety and efficacy.

Stage 1 (75 mg/day)
Enroll 10

- If safe but not effective, go to Stage 2
- If safe and effective, go to Stage 4
- If not safe but effective, go to Stage 4
- If not safe and not effective, **end study**.

Stage 2 (100 mg/day)
Enroll 10

- If safe but not effective, go to Stage 3.
- If safe and effective, declare 100 mg/day a safe dose and enroll expansion cohort at 100 mg/day.
- If not safe but effective, declare 75 mg/day a safe dose and enroll expansion cohort at 75 mg/day.
- If not safe and not effective, pool data from Stages 1 and 2 to determine whether or not ≥ 40% demonstrate reduction in EGFR staining (definition of effective). If still not effective, **end study**. If effective, declare 75 mg/day a safe dose and enroll expansion cohort at 75 mg/day.

Stage 3 (150 mg/day)
Enroll 10

- If safe but not effective, **end study.**
- If safe and effective, declare 150 mg/day a safe dose and enroll expansion cohort at 150 mg/day.
- If not safe but effective, pool data from Stages 2 and 3 to determine whether or not > 33% demonstrate a DLT. If total % DLT is < 33%, declare 100 mg/day a safe dose and enroll expansion cohort at 100 mg/day.
- If not safe and not effective, pool data from Stages 2 and 3 to determine whether or not ≥ 40% demonstrate reduction in EGFR staining (definition of effective). If still not effective**, end study**. If effective, declare 100 mg/day a safe dose and enroll expansion cohort at 100 mg/day.

Stage 4 (50 mg/day)
Enroll 10

- If safe and effective, go to Stage 5.
- If safe but not effective, declare 75 mg/day a safe dose and enroll expansion cohort at 75 mg/day.
- If not safe but effective, pool data from Stages 1 and 4 to determine whether or not > 33% demonstrate a DLT. If total % DLT is < 33%, declare 50 mg/day a safe dose and enroll expansion cohort at 50 mg/day.
- If not safe and not effective, pool data from Stages 1 and 4 to determine whether or not ≥ 40% demonstrate reduction in EGFR staining (definition of effective). If still not effective, **end study**. If effective, declare 75 mg/day a safe dose and enroll expansion cohort at 75 mg/day.

Stage 5 (25 mg/day)

Enroll 10

- If safe but not effective, declare 50 mg/day a safe dose and enroll expansion cohort at 50 mg/day.
- If safe and effective, declare 25 mg/day a safe dose and enroll expansion cohort of 20 at 25 mg/day.
- If not safe but effective, pool data from Stages 4 and 5 to determine whether or not > 33% demonstrate a DLT. If total % DLT is < 33%, declare 25 mg/day a safe dose and enroll expansion cohort at 25 mg/day.
- If not safe and not effective, pool data from Stages 4 and 5 to determine % DLT and % reduction in EGFR staining (definition of effective). If safe, enroll expansion cohort at 25 mg/day.

Minimum enrollment = 10; if 75 mg/day deemed not safe (after < 3 cohorts of 5) and not effective.

Maximum enrollment = 45; if 25 mg/day deemed safe and expansion cohort enrolled.