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Phase II Trial of Weekly Erlotinib Dosing to Reduce Duodenal Polyp Burden Associated with Familial Adenomatous Polyposis

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SCHEMA

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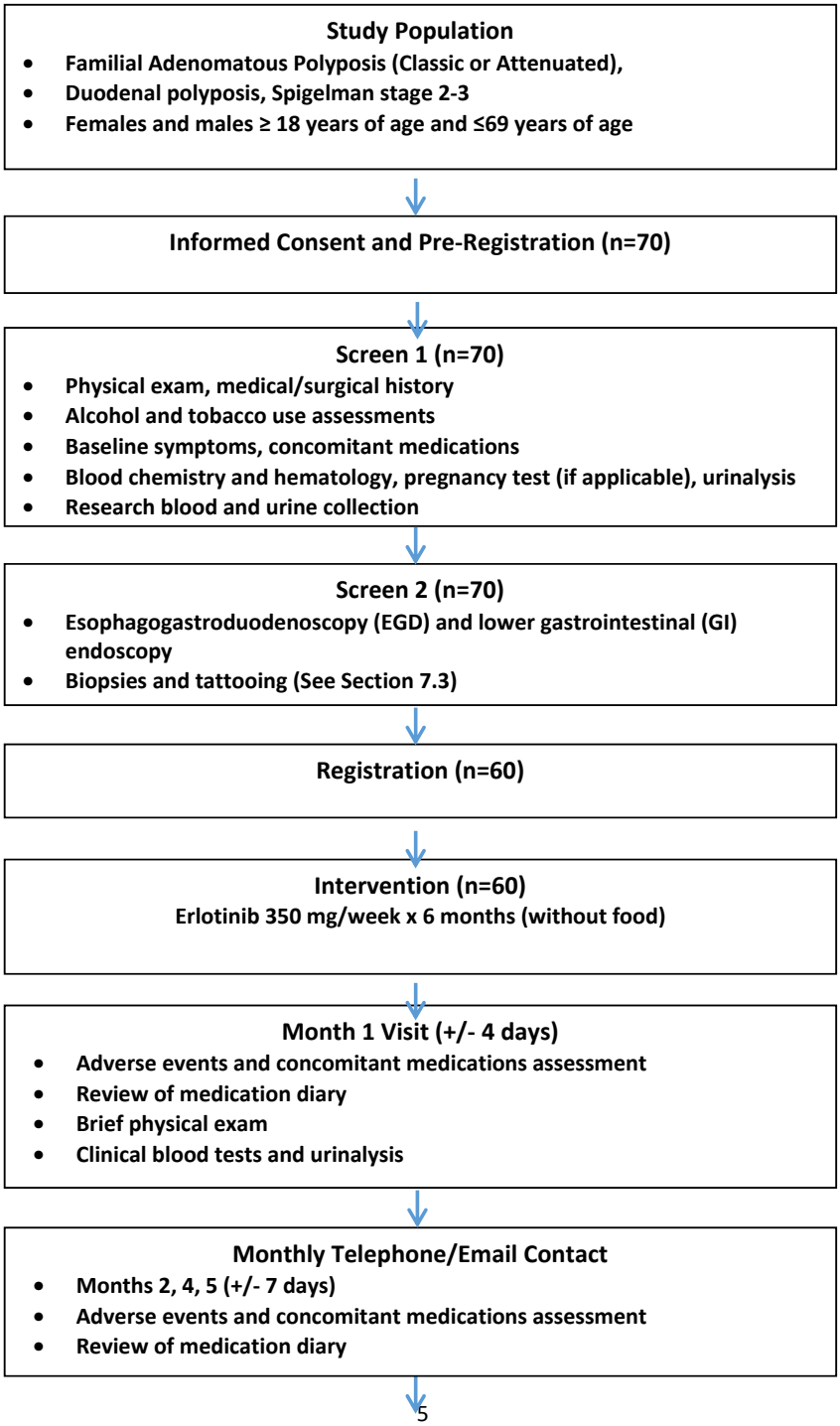

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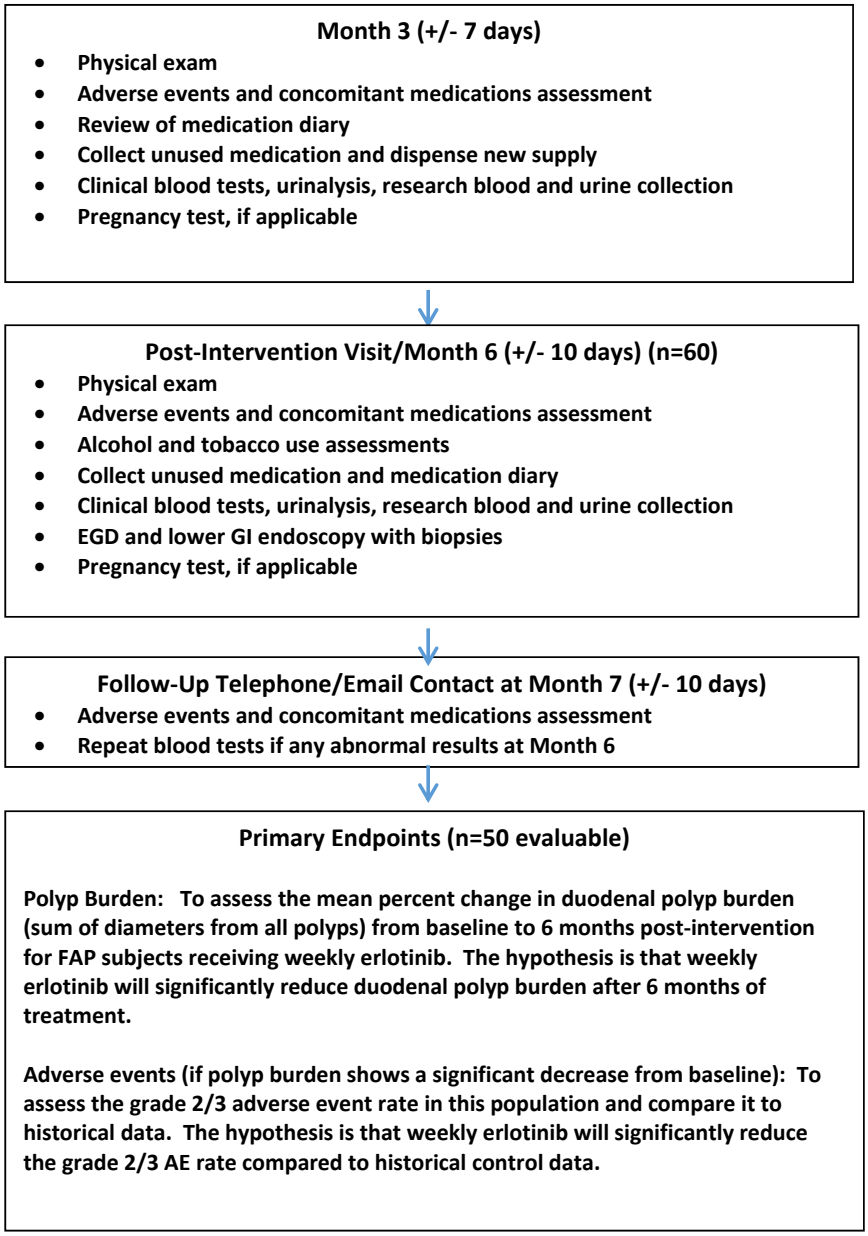

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1. OBJECTIVES

1.1 Primary Objectives

- Polyp Burden: To assess the mean percent change in duodenal polyp burden (sum of diameters from all polyps) from baseline to 6 months post-intervention for FAP subjects receiving weekly erlotinib. The hypothesis is that weekly erlotinib will significantly reduce duodenal polyp burden after 6 months of treatment.
- Adverse events (if polyp burden shows a significant decrease from baseline): To assess the grade 2/3 adverse event rate in this population and compare it to historical data. The hypothesis is that weekly erlotinib will significantly reduce the grade 2/3 AE rate compared to historical control data.

1.2 Secondary Objectives

- To evaluate all adverse events at least possibly attributed to weekly erlotinib;
- To assess the absolute and percent change in duodenal polyp number from baseline to 6 months;
- To assess the absolute and percent changes in lower gastrointestinal polyp burden and number for the subset of participants with ileal pouch anal anastomosis (IPAA) or ileo-rectal anastomosis with rectal stump (anticipated to be approximately 70% of registered cohort); and
- To assess the absolute and percent change in desmoid tumor size in participants who have baseline and follow up CTs performed as part of their standard of care (anticipated to be approximately 30% of the registered cohort);
- Gene expression profiles in duodenal adenomas and uninvolved tissue will be compared between baseline and endpoint samples using negative binomial statistics (DESeq2):
    - Identify differentially expressed genes between duodenal polyps and uninvolved tissue at endpoint compared to baseline;
    - Evaluate the effect of weekly erlotinib on EGFR and Wnt target gene expression in duodenal adenomas;
    - Evaluate the effect of weekly erlotinib on immune response signaling in duodenal adenomas and uninvolved tissue.

2. BACKGROUND

2.1 Familial Adenomatous Polyposis (FAP)

Multiple studies have shown that the cyclooxygenase (COX) inhibitor, sulindac, a nonsteroidal anti-inflammatory drug (NSAID), significantly inhibits colorectal adenomatous polyps in FAP patients.[1, 2] However, NSAIDs have demonstrated considerably less efficacy with respect to duodenal adenoma burden, based on a limited number of studies to date.[3, 4] Celecoxib use resulted in a modest reduction of duodenal[5] and

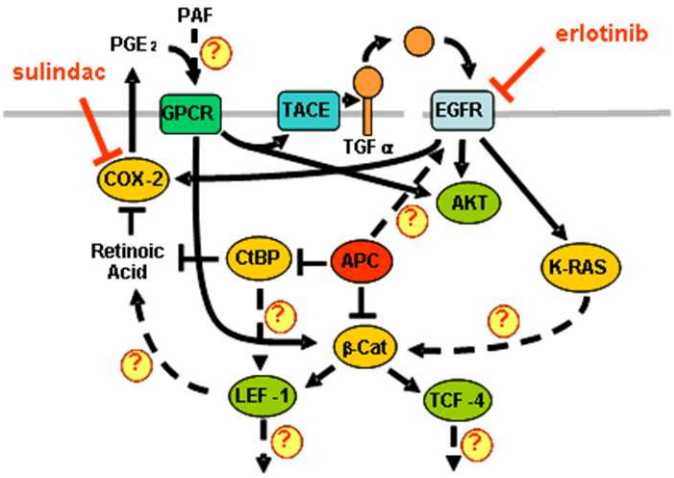

Figure 1. Effects of sulindac and erlotinib on signaling pathways, based on studies to date.

colorectal polyps,[6, 7] but is no longer FDA-approved for this indication.[8] Studies have suggested that APC inactivation and epidermal growth factor receptor (EGFR) signaling promote COX-2 expression and the subsequent development of intestinal neoplasia.[9, 10] Convergence between the *Wnt* and EGFR signaling pathways and COX-2 activity was demonstrated in a mouse model of FAP, in which a combination of sulindac and an EGFR inhibitor diminished small intestinal adenoma development by 87%.[11] Normally, *APC* down-regulates β–catenin through a complex with Axin, CK1, and GSK-3β. Mutational inactivation of *APC* results in the accumulation and nuclear translocation of β–catenin where it interacts with TCF-4/LEF-1 transcription factors to activate genes whose products mediate proliferation, survival, and migration. Despite the fact that *APC* is mutated in the vast majority of colorectal adenomas and adenocarcinomas in humans, careful examination of human colorectal tumors in multiple studies have shown that nuclear β–catenin is found in only a small minority of microscopic and larger adenomas, compared with approximately half of adenocarcinomas. Thus, constitutive activation of the canonical WNT signaling pathway appears to increase progressively during the adenoma-carcinoma sequence in the gut. However, the molecular events downstream of *APC* mutation at the early stages of neoplastic transformation are not entirely explained by the current model. Prior studies from our group document that germline mutation of *apc* in zebrafish leads to a loss of retinoid synthesis in colorectal tissue early in the formation of polyps. This loss of retinoid expression is β–catenin-independent and results in the up-regulation of cyclo-oxygenase 2 (COX-2) in intestinal tissue (see **Figure 1**). COX-2 has been shown to drive the expression and release of growth factors, such as TGFα, and inflammatory mediators (prostaglandins, thromboxane, and prostacyclin), and, is a key target of chemopreventive agents. An important target downstream of COX-2 is the epidermal growth factor receptor (EGFR). Preliminary and previous studies by Jones *et al.* show that germline *APC* mutation alone is insufficient to cause nuclear localization of β–catenin and hence canonical WNT signaling in preneoplastic intestinal tissue and early adenomas. Jones *et al.* showed that co-activation of EGFR-RAS-MEK signaling is required for the nuclear localization of β–catenin. Furthermore, EGFR activation increases COX-2 expression leading to reinforcement of EGFR activation and signaling. Progressive mutational events, namely, loss of heterozygosity of *APC* and oncogenic activation of *KRAS*, further reinforce COX-2 and EGFR signaling crosstalk.

FAP patients are at greatly increased risk for duodenal neoplasia, with duodenal adenomas eventually forming in >50% of FAP patients and duodenal adenocarcinoma occurring in up to 12%.[12-17] In fact, following colectomy, duodenal adenocarcinoma is the leading cause of cancer death in FAP patients. Unfortunately, endoscopic and surgical interventions are often challenging and suboptimal with respect to preventing invasive malignancy.[18, 19] Therefore, it is imperative that more effective duodenal cancer prevention/control strategies be developed for patients with FAP. Building on positive findings from the recently completed FAPEST trial, further definition of an effective, well-tolerated dosing regimen for erlotinib could favorably impact FAP standard of care with consequent improvements in morbidity, mortality, and quality of life.

2.2 Erlotinib (Tarceva® NDA-021743)

Erlotinib (Tarceva®, NDA-021743), an FDA-approved tyrosine kinase inhibitor, directly and reversibly inhibits the human EGFR tyrosine kinase with an IC_{50} of 2 nM (0.79 ng/mL) in an *in vitro* enzyme assay and reduces EGFR autophosphorylation in intact tumor cells with an IC_{50} of 20 nM (7.9 ng/mL). This potent inhibition is selective for the EGFR tyrosine kinase. Standard targeted therapy dosing ranges from 100-150 mg/day, based on pharmacokinetic studies showing an average plasma concentration of 500ng/mL, which is targeted for clinical efficacy when treating existing cancer.

2.3 Rationale

In our prior "Clinical Trial of COX and EGFR Inhibition in Familial Polyposis Patients" trial (FAPEST; NCT01187901), erlotinib at 75 mg/day was investigated and found to be associated with marked duodenal neoplasia regression (further described in section I) recently published in the Journal of the American Medical Association.[20] However, agent tolerability was limited by acneiform rash and oral mucositis. This resulted in dose reductions, leading to FAPEST participants receiving an average erlotinib dose of 50 mg/day. Another recent clinical trial in individuals with advanced premalignant head and neck lesions determined that erlotinib 50 mg/day was the maximum tolerated dose with minimal observed toxicity yet retained histologic remission.[21] Preclinical [22] and early phase clinical trial[23, 24] data suggest that intermittent, once weekly dosing of erlotinib (seven times the daily dose) yields clinical efficacy with fewer adverse effects, offering intriguing potential for chemopreventive application. Based on these findings, we propose to evaluate the efficacy and tolerability of erlotinib 350 mg/week as a candidate intervention for duodenal polyp regression in patients with familial adenomatous polyposis (FAP).

Increasing evidence suggests that tobacco and alcohol use are risk factors in the development of intraepithelial neoplasia and cancer. In addition, tobacco and alcohol use may adversely affect agent intervention, for example by altering the safety profile or metabolism of a drug. Standardized assessments of tobacco and alcohol use during clinical trials will aid in understanding the potential relationship between the use of these products and clinical endpoints or cancer prevention biomarkers. Therefore, NCI, DCP is including assessment of tobacco and alcohol use at baseline and Month 6, to determine the potential impact of tobacco and alcohol use on 1) treatment toxicity and symptom burden, and 2) the efficacy of treatment intervention.

3. SUMMARY OF STUDY PLAN

General overview: We will evaluate the efficacy and toxicity of a 6-month intervention of erlotinib 350 mg/week in FAP patients (see Schema). Change in duodenal polyp burden (comparing post-intervention vs. baseline) will be assessed by esophagogastroduodenoscopy (EGD), utilizing field tested measurement protocols applied in our recently completed FAPEST study, and will serve as the primary endpoint. Adverse events will be monitored and reported according to NCI CTCAE v. 4.0 criteria. The proposed trial will also provide a unique opportunity to generate novel data regarding the RNA transcriptome in FAP patients, based on RNA sequencing (RNA-Seq) technology. RNA-Seq will be performed on uninvolved duodenal mucosal biopsy specimens obtained at the baseline and post-intervention EGD exams (placed in RNA Later and stored at -80°C prior to RNA isolation). These molecular studies will facilitate characterization of participant response at the cellular level and will also offer new insights pertaining to the molecular mechanisms of duodenal polyp growth/regression. Additional changes in duodenal and colorectal polyps will also be measured and compared between intervention arms as secondary endpoints.

Baseline Evaluation: Prior to registration, willing, consented participants will be screened in two stages, as outlined below.

Screening 1: Individuals with FAP (classic or attenuated) will be identified from clinical practice and existing registries. Willing, eligible trial participants will be consented (see Schema) and will undergo

physical exam; medical/surgical history; alcohol and tobacco use assessment; blood chemistry and hematology testing; pregnancy test, if applicable; symptom and concomitant medication assessments; urinalysis, and research blood draw and urine collection.

Screening 2: Esophagogastroduodenoscopy (EGD) will be performed to evaluate the duodenum using forward-viewing and/or side-viewing techniques (with still and video documentation).

A tattoo will be placed 10 cm distal to the duodenal bulb to define a region heretofore referred to as the *duodenal segment*, which will extend from the duodenal bulb distally to point of the tattoo. Endoscopic tattooing has been widely employed in previous research protocols and is clinically advocated by many authorities.[25, 26] For willing participants who are undergoing lower endoscopy for clinical purposes, rectal/pouch polyps may also be measured and recorded.

During the baseline endoscopy procedures, one polyp will be sent to the local pathology laboratory for histological analysis, since this assessment is an inherent component of the Spigelman stage categorization for duodenal polyps. Remaining polyps will be sampled but not removed (unless clinically required) from the 10 cm duodenal segment and rectum/pouch. Any lesions containing high-grade dysplasia or cancer will result in study exclusion and will be managed with appropriate surgical or oncology referral(s). All endoscopy exams will be recorded in high definition using Medicapture (or comparable) recorders to allow for blinded review as a future secondary endpoint.

On Study: 60 eligible participants will be assigned to an intervention of erlotinib 350 mg once weekly without food. Study agents will be self-administered for a period of 6 months. Participants will return for a visit at Month 1 (+/- 4 days) for brief physical exam, adverse events assessment (especially weakness, fatigue, rash, diarrhea, abdominal pain, melena, hematochezia, nausea, vomiting), concomitant medications review, and blood and urine tests. Participants will be contacted monthly (Months 2, 4, and 5) by the study coordinator to ensure medication compliance and record adverse events. A diary of compliance and symptoms will be maintained by participants and reviewed during an office visit at 3 months (+/- 7 days). The Month 3 study visit will also include a physical exam, urinalysis, pregnancy test (if applicable), and blood draw for safety and toxicity monitoring, as well as research. Concomitant medications, adverse events, and medication compliance will also be reviewed. Throughout the intervention period, participants will be provided with “adverse event medications” to counteract anticipated symptoms associated with the study agents, based on observations from the FAPEST study.

Post-Intervention: At the Month 6 visit (+/- 10 days) or early termination, participants undergo a physical exam, adverse event and concomitant medication assessments, laboratory studies, urinalysis, repeat pregnancy test (if applicable), follow up alcohol and tobacco use assessments, and research blood draw and urine collection. EGD and lower GI endoscopy with biopsies will be performed according to the same protocols applied at baseline. A follow up phone call will take place at month 7 (+/- 10 days) to assess adverse events and repeat any blood tests that were outside of institutional limits of normal at Month 6. Any reported SAEs will be followed to resolution.

4. PARTICIPANT SELECTION

4.1 Pre-Registration Inclusion Criteria

4.1.1 Diagnosis of familial adenomatous polyposis (FAP) or attenuated familial adenomatous polyposis (AFAP), defined as at least one of the following:

- Genetic diagnosis with confirmed APC mutation (clinical CLIA certified lab or research testing)
- Obligate carrier
- Clinical diagnosis of classic FAP with ≥ 100 colorectal adenomas status post colectomy and a family history of FAP
- Clinical diagnosis of FAP, based on personal and family history. Note: This criterion requires documented review and agreement from either the Study Chair or the CPN Lead Investigator.

4.1.2 Age ≥18 and ≤69 years of age. Note: Because no dosing or adverse event (AE) data are currently available on the use of erlotinib in participants <18 years of age, children are excluded from this study but will be eligible for future pediatric trials, if applicable.

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

4.1.4 Willing to discontinue taking NSAIDS for 30 days prior to initiation of and during intervention. Exception: Use of ≤ 81 mg daily or ≤ 650 mg weekly aspirin is allowed.

4.1.5 Willing to discontinue smoking for the duration of study intervention

4.1.6 Willing to provide mandatory biospecimens as specified in the protocol

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 History of allergic reactions attributed to compounds of similar chemical or biologic composition to erlotinib

4.2.3 Use of potent CYP3A4 inhibitors, including but not limited to ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice

4.2.4 Use of potent CYP3A4 inducers, including but not limited to rifampicin, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital, and St. John's Wort

4.2.5 Use of any other investigational agents ≤ 12 weeks prior to pre-registration.

4.2.6 Uncontrolled intercurrent illness or recent surgical procedure that in the opinion of the investigative team would limit compliance with study requirements, including, but not limited to:

- Ongoing or active infection

- Symptomatic congestive heart failure
- Myocardial infarction ≤ 6 months prior to intervention
- Severely impaired lung function
- Nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with study intervention
- Diagnosed liver disease, such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis
- Unstable angina pectoris
- Cardiac arrhythmia
- Psychiatric illness/social situations

4.2.7 History of invasive malignancy ≤ 3 years prior to pre-registration. Exception: adequately treated carcinoma of the cervix, carcinoma in situ, or basal or squamous cell carcinomas of the skin.

4.2.8 Individuals on anticoagulation medications who cannot safely discontinue the medication for at least 48 hours prior to the study endoscopy, as determined by the study investigator and/or participant's primary healthcare provider.

4.2.9 History of any upper GI surgery that does not permit access to or evaluation of a 10 cm segment of the duodenum that includes the duodenal bulb, i.e. Whipple Procedure or similar

4.3 Registration Inclusion Criteria

4.3.1 ECOG performance status ≤1 (See Appendix A)

4.3.2 Adequate bone marrow and organ function:

- Leukocytes (WBC) ≥ 3,000/uL (≥ 2,500/uL for African-American participants)
- Platelet count ≥ 100 x 10^9/L
- Hemoglobin ≥ 11.5 g/dL
- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
- Alkaline phosphatase ≤ 1.5 x institutional upper limit of normal (ULN)
- AST/SGOT ≤ 2 x institutional upper limit of normal (ULN)
- ALT/SGPT ≤ 2 x institutional upper limit of normal (ULN)
- Creatinine ≤ institutional upper limit of normal (ULN)
- Urinary testing results within institutional limits of normal or deemed clinically insignificant.

4.3.3 Spigelman 2-3

4.3.4 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. Breastfeeding should be discontinued if the mother is treated with erlotinib.

4.3.5 Willing to use adequate contraception to avoid pregnancy or impregnation until 2 weeks after discontinuing study agent

4.4 Registration Exclusion Criteria

4.4.1 Histologically-confirmed high grade dysplasia (HGD), cancer, or polyp burden that is not quantifiable.

4.4.2 Regular (≥ 2 times per week) use of 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 replace the PPI with an H2 receptor agonist, i.e. ranitidine, for the duration of the trial will be eligible. See Section 5.5 for details.

4.4.3 Gastrointestinal bleeding. Note that the presence of any symptoms (dyspnea, fatigue, angina, weakness, malaise, melena, hematochezia, hematemesis, anemia, abdominal pain) will require clinical assessment to rule out gastrointestinal bleeding.

4.5 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial. Participants may be English-speaking or non-English-speaking. 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 Worksheet 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 quarterly, at a minimum, in accordance with a master accrual target plan developed cooperatively between the CPN and DCP teams.

In general, site 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 existing hereditary gastrointestinal cancer registries, clinical referral, family expansion, and self-referral. In all cases, only individuals who have consented to being contacted for future research will be contacted regarding this clinical trial. The trial will be posted on clinicaltrials.gov and, if applicable, each of the institutions' clinical trial web sites. Participant consent, screening, and study visits will be implemented per protocol and per institutional policies and procedures. Study teams will maintain contact participants per protocol to improve compliance, retention, and adherence.

5. AGENT ADMINISTRATION

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

5.1 Dose Regimen and Dose Groups

Erlotinib (Tarceva®), 350 mg once per week for 6 months.

5.2 Erlotinib Administration

- Participants will be dispensed erlotinib at the time of Registration and at the Month 3 visit.
- At each time point, participants will be dispensed 30 tablets of erlotinib 150 mg and 30 tablets of erlotinib 25 mg.
- Participants will self-administer one weekly dose consisting of two 150 mg tablets and two 25 mg tablets. If a dose reduction is indicated (see Section 5.6), the participant will take one 150 mg tablet and one 25 mg erlotinib tablet.
- Erlotinib will be taken with 200 mL of water on the same day and approximately the same time each week. This will be done at least one hour before or two hours after any food intake.

5.3 Run-in Procedures

There will be no run in procedures.

5.4 Contraindications

- Smoking (Urine cotinine testing will be done pre- and post-intervention to monitor exposure to smoke)
- Medications that alter the pH of the upper GI tract, such as PPIs and antacids

5.5 Concomitant Medications

Patients who are being concomitantly treated with potent CYP3A4 inducers will not be eligible for this study. Potent CYP3A4 inhibitors include, but are not limited to ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice. Potent CYP3A4 inducers include but are not limited to rifampicin, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital, and St. John's Wort.

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 (PPI), 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. Individuals who take prescription PPIs at the time of registration, who, in the clinical judgement of the investigator, can safely transition off the PPI to an H2 receptor agonist (i.e. ranitidine), and can tolerate not taking the H2 blocker on the day before and the day of erlotinib dosing can be eligible.

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 anticoagulants will be excluded from study participation if, in the opinion of the study investigator and/or primary health care provider, they cannot safely discontinue the medications for at least 48 hours prior to the endoscopy procedures.

Patient must discontinue taking any NSAIDS (including sulindac) within thirty days (30 days) of treatment initiation. However, patients using 81 mg daily aspirin or 650 mg aspirin not more than once a week are eligible.

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the concomitant medication CRF and will include: 1) start and stop date, dose and route of administration, and indication. Medications taken for a procedure (*e.g.*, biopsy) should also be included.

5.6 Dose Modification

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Dose reduction or interruption of erlotinib for toxicity may take place at any time during the study at the discretion of the investigator. Toxicity grading is based on NCI-CTCAE, v 4.0. Dose level reductions are presented in **Table 1**. If participants do not tolerate the second erlotinib dose reduction, treatment is to be discontinued.

Table 1
Dose Level Reductions

Drug	Starting Dose	First Reduction	Second Reduction
Erlotinib	350 mg once per week	175 mg once per week	0 mg/week (intervention holiday)

Erlotinib specific toxicities:
Dose reductions may be implemented at the discretion of the investigator. At the discretion of the treating physician and when it is in the best interests of the study participant, a dose holiday can be implemented even prior to a dose reduction. Recommendations for dose reductions due to adverse events are as follows:

All study participants will be advised to use loperamide or comparable medication at the earliest onset of diarrhea. All study participants will be provided with prescriptions for alcohol-free emollient cream, oral antibiotics (tetracycline, minocycline, or doxycycline), topical clindamycin, diphenhydramine, topical or oral corticosteroids at discretion of investigator. These are to be used as needed to manage expected symptoms. It is estimated that approximately 30% of participants may require eye drops or stronger antibiotics for symptom management.

Management of a tolerable Grade 2 or 3 rash should include continuation of erlotinib at the current dose and symptomatic management. If skin rash is intolerable, dose reduction according to Table 2 should be considered. When skin toxicity improves by at least one grade level, the dose may be re-escalated as tolerated. In Phase II trials, this approach enabled dose re-escalation for the majority of participants requiring dose reduction for skin toxicity. Participants experiencing Grade 4 skin toxicity should be discontinued from study treatment.

A detailed flow diagram for management of erlotinib-related rash is available on the CPN website at this location: https://cancerpr.ipower.com/member/MAY2016-07-01.shtml See Protocol Section 8.3 for information regarding follow-up activities for participants who, due to adverse events, must discontinue study agent before study completion.

For Grade 1 or 2 diarrheas, early intervention should include continuation of erlotinib at the current dose and initiation of loperamide therapy as described in **Table 2**. Grade 2 diarrhea that persists over 48–72 hours, despite optimal medical management, should be managed by dose reduction according to **Table 2**. Participants experiencing Grade 3 diarrhea should interrupt erlotinib until resolution to Grade ≤1 and re-start at a reduced dose according to **Table 2**. Participants should be maintained at the reduced dose without attempt at dose re-escalation. Participants experiencing Grade 4 diarrhea should be discontinued from study treatment.

Erlotinib should not be restarted in those suspected of having drug-related interstitial lung disease (ILD). For any participants being taken off study due to a SAE, the issue will be reported as described in Section 11.2.

Table 2. Dosage Modification Criteria and Guidelines for Management of Erlotinib -Related Toxicities

NCI-CTCAE (v 4.0) Grade	Erlotinib Dose Modification	Guideline for Management
Diarrhea		
Grade 1	None	Consider loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until free of diarrhea for 12 hours)
Grade 2	None (Dose reduction of erlotinib is necessary if diarrhea persists over 48–72 hours despite optimal medical management)	Loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until diarrhea free for 12 hours)
Grade 3	Interrupt then dose reduce erlotinib. Erlotinib should not be re-escalated.	Interrupt erlotinib until resolution to Grade ≤1, and restart at next reduced dose
Grade 4	Discontinue study treatment.	
Pulmonary Events (if possibly ILD)		
All Grades	Temporarily interrupt erlotinib pending the diagnostic evaluation. If the pulmonary adverse event is assessed as related to erlotinib, discontinue the participant from study treatment.	Unexplained dyspnea, either new or progressive, should be aggressively evaluated.
Rash		
Grade 1 and 2 and Tolerable rash	None	Any of the following: alcohol-free emollient cream, oral antibiotics (tetracycline, minocycline, doxycycline) topical clindamycin, diphenhydramine, topical or oral corticosteroids at discretion of investigator
Grade 3 or Intolerable rash	Consider interruption and or dose reduction if unresponsive to symptomatic management. Re-escalation is allowed.	Manage as described above
Grade 4	Discontinue study treatment.	Manage as described above

5.7 Adherence/Compliance

5.7.1 Participant compliance with study visit and requirements will be documented. Compliance with taking study medications will be documented via the use of medication diaries and recorded on case report forms for appropriate subgroup statistical analysis.

5.7.2 Participants will be required to complete and submit medication diaries. Dispensed and returned medication will be accounted for according to DCP and Participating Organization policies and procedures.

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6. PHARMACEUTICAL INFORMATION

6.1 Erlotinib (IND#: 64808, IND Sponsor: NCI, DCP)

Clinical studies investigating the chemopreventive efficacy of erlotinib are conducted under IND 64808 sponsored by NCI, DCP. Erlotinib (Tarceva®) is an epidermal growth factor receptor (EGFR) inhibitor approved by the FDA as a targeted therapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletion or exon 21 (L8568R) substitution mutation, 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 for OSI Pharmaceuticals, LLC by Astellas Pharma US (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 and 150 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

Safety evaluation of erlotinib is based on more than 1200 cancer patients who received erlotinib as a targeted therapy, more than 300 patients who received 100 or 150 mg erlotinib plus gemcitabine, and 1228 patients who received erlotinib concurrently with other cancer treatments. The most common adverse reactions with erlotinib are rash and diarrhea usually with onset during the first month of treatment. The incidences of rash and diarrhea from clinical studies of erlotinib for the treatment of NSCLC and pancreatic cancer were 70% for rash and 42% for diarrhea.

In first-line treatment of NSCLC patients with EGFR mutations, the most frequent (≥30%) adverse reactions in erlotinib-treated patients were diarrhea, asthenia, rash, cough, dyspnea, and decreased appetite. Adverse events occurring in 4–20% of erlotinib-treated patients included pruritus, dry skin, and paronychia. The median time to onset of rash was 15 days and the median time to onset of diarrhea was 32 days. The most frequent grade 3/4 adverse reactions were rash and diarrhea. Dose interruptions or reductions due to adverse reactions occurred in 37% of erlotinib-treated patients, and 14.3% of erlotinib-treated patients discontinued therapy due to adverse reactions. In erlotinib-treated patients, the most frequently reported adverse reactions leading to dose modification were rash (13%), diarrhea (10%), and asthenia (3.6%). One erlotinib-treated patient experienced fatal hepatic failure and four additional patients experienced grade 3/4 liver test abnormalities in the first-line, randomized, open-label clinical trial of erlotinib in NSCLC.

As maintenance treatment in patients with locally advanced or metastatic NSCLC whose disease did not progress during first-line platinum-based chemotherapy, the most common adverse reactions in patients receiving single-agent 150 mg erlotinib were rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 9% and 2%, respectively, in erlotinib-treated patients. Rash and diarrhea resulted in study discontinuation in 1% and 0.5% of erlotinib-treated patients, respectively, and dose reduction or interruption for rash and diarrhea was needed in 5% and 3% of patients, respectively. In erlotinib-

treated patients the median time to onset of rash was 10 days, and the median time to onset of diarrhea was 15 days. Liver test abnormalities including alanine aminotransferase (ALT) elevations were observed at grade 2 or greater severity in 3% of erlotinib-treated patients and 1% of placebo-treated patients. Grade 2 and above bilirubin elevations were observed in 5% of erlotinib-treated patients and in <1% in the placebo group.

In a study comparing first-line maintenance therapy with erlotinib administered at the time of disease progression in late-stage NSCLC, 11 deaths due to AEs occurred in patients who received erlotinib (pulmonary embolism [3 patients], pneumonia [2 patients], cardio-respiratory arrest, cardio-pulmonary failure, metabolic acidosis, cerebrovascular accident, hemoptysis, aspiration pneumonia) compared with 3 patients who received placebo (lobar pneumonia, hydrocephalus, respiratory failure).

In a study of erlotinib in second- and third-line treatment of NSCLC, the most common adverse reactions were also rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 9% and 6%, respectively, in erlotinib-treated patients. Rash and diarrhea each resulted in study discontinuation in 1% of erlotinib–treated patients, and 6% percent and 1% of patients needed dose reduction for rash and diarrhea, 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 ALT, aspartate aminotransferase [AST], and bilirubin) were observed in patients receiving single-agent erlotinib at 150 mg. These elevations were mainly transient or associated with liver metastases. Grade 2 (>2.5–5.0 × ULN) ALT elevations occurred in 4% and <1% of erlotinib and placebo treated patients, respectively. Grade 3 (>5.0–20.0 × ULN) elevations were not observed in erlotinib-treated patients.

The most common AEs in pancreatic cancer patients receiving 100 mg erlotinib plus gemcitabine were fatigue, rash, nausea, anorexia, and diarrhea; less common AEs included weight loss. 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 1% 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. 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 × ULN) ALT elevations in 31% and grade 3 (>5.0–20.0 × 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, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections.

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 disease or concomitant treatment with potentially hepatotoxic drugs. The pooled incidence of hepatic failure in the three monotherapy lung cancer studies, where patients with moderate to severe hepatic impairment were excluded, was 0.4% in the erlotinib arms and 0% in the control arms. The incidence of hepatic failure in the pancreatic cancer study was 0.4% in the erlotinib plus gemcitabine arm and 0.4% in the control arm.

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. Gastrointestinal perforation, including fatal cases, have been rarely reported with erlotinib treatment. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, or taxane-based chemotherapy, or who have prior history of peptic ulceration or diverticular disease may be at increased risk of perforation. The pooled incidence of gastrointestinal perforation in the three monotherapy lung cancer studies was 0.2% in the erlotinib arms and 0.1% in the control arms. The incidence of gastrointestinal perforation in the pancreatic cancer study was 0.4% in the erlotinib plus gemcitabine arm and 0% in the control arm.

Corneal ulcerations or perforations have been reported in patients receiving erlotinib. Decreased tear production, abnormal eyelash growth, keratoconjunctivitis sicca, and keratitis have been reported and are risk factors for corneal ulceration/perforation. Hair and nail changes, mostly non-serious, were reported; paronychia was reported commonly and hirsutism, eyelash/eyebrow changes, and brittle and loose nails were reported uncommonly. Bullous, blistering, and exfoliative skin conditions, including cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, which in some cases were fatal, can occur with erlotinib treatment. The pooled incidence of bullous and exfoliative skin disorders in the three monotherapy lung cancer studies was 1.2% in the erlotinib arms and 0% in the control arms. The incidence of bullous and exfoliative skin disorders in the pancreatic cancer study was 0.4% in the erlotinib plus gemcitabine arm and 0% in the control arm.

In the pancreatic carcinoma trial, six patients (incidence 2.1%) 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 1.1%) and one died due to myocardial infarction. In the same trial, seven patients in the

erlotinib/gemcitabine group developed cerebrovascular accidents (incidence 2.5%). One of these was hemorrhagic and was the only fatal event. In contrast, there were no cerebrovascular accidents in the placebo/gemcitabine group. The pooled incidence of microangiopathic hemolytic anemia with thrombocytopenia in the three monotherapy lung cancer studies was 0% in the erlotinib arms and 0.1% in the control arms. The incidence of microangiopathic hemolytic anemia with thrombocytopenia in the pancreatic cancer study was 1.4% in the erlotinib plus gemcitabine arm and 0% in the control arm. Other mild skin reactions, such as hyperpigmentation, have been observed uncommonly (in <1% of patients).

In the previously reported FAPEST study, 83% of participants experienced Grades 1-3 adverse events. There were no Grade 4 or 5 events. The most common adverse event was an erlotinib-induced acneiform-like rash, which occurred in 87% of the treatment group (n=40) and 20% of the placebo group (n=9) (*P* < .001). The rash was managed with topical cortisone and/or clindamycin therapy. Additional adverse events commonly increased in the treatment group included oral mucositis (39.1%; n=18), diarrhea (26%; n=12), and nausea (23.9%; n=11). Of the participants who completed the study, 73% had erlotinib dose reductions due to grade 1 and 2 rash that were deemed intolerable by the participants.[20]

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 discontinuing erlotinib. 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 while taking erlotinib. 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 CYP1A2, and in the lungs by CYP1A1. A potential for drug-drug interaction exists when erlotinib is coadministered 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 will be excluded.

6.3 Availability

Erlotinib will be obtained from Astellas by NCI, DCP 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 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 Drug Accountability Record Form (DARF). The Investigator is required to maintain adequate records of receipt, dispensing and final disposition of study agent. This responsibility has been delegated to each sites' licensed pharmacy staff as listed on the site-specific Delegation of Tasks document. 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.

6.6 Packaging and Labeling

Erlotinib is packaged in high density polyethylene bottles, each containing thirty (30) tablets. Erlotinib will be supplied in two bottles, one containing thirty (30) 150mg tablets and one containing thirty (30) 25mg tablets, and will be labeled with the following content: product identification and strength, NSC number, tablet count, lot/batch number, expiration date, name and address of manufacturer, storage information, investigational use language (Caution: New Drug Limited by Federal Law to Investigational

Use Only. Keep out of reach of children"), and instructions to take as directed. Prior to dispensing investigational product, trial personnel will attach a label containing the participant identification number, randomization number, and dispensing date.

6.7 Storage

Erlotinib tablets (150 mg and 25 mg) are supplied in high density, polyethylene bottles and should be stored in a secure location. Storage will be maintained at 25° C (77°F); excursions permitted to 15°C - 30°C (59°F - 86°F). See USP Controlled Room Temperature.

6.8 Pre-Registration and Registration

6.8.1 Participant Pre-Registration

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; Email: Random01@mayo.edu). The CPN Registration Office will enter the data into the CPN-hosted database.

6.8.1.2 At the time of pre-registration, the following will be verified:

- CIRB approval (local context subcommittee) and IRB acknowledgement of CIRB approval and informed consent at the registering institution
- Participant eligibility (including existence of a signed informed consent document)
- Existence of a signed authorization for use and disclosure of protected health information (USA Institutions only).
- Study agent is available and Drug Shipment Authorization has been granted to the registering site.

The following will also be recorded:

- Participant has/has not given permission to collect and store blood, urine, and/or tissue specimens and related information in a Biobank for future use in research to learn about, prevent, treat, or cure cancer and other health problems.
- Participant has/has not given permission to contact him/her or his/her physician to learn about the results of these studies.
- Participant has/has not given permission to send blood, urine, and/or tissue specimens and related information to researchers at outside institutions.
- Participant has/has not given permission for information from the alcohol and tobacco use assessment to be used in future health research.
- Participant has/has not given permission to his/her doctor or their representative to ask them if they wish to participate in other research in the future.

6.8.1.3 Baseline (screening) evaluations must be completed within the guidelines specified on the Schedule of Events (See Section 7.1).

6.8.1.4 Registration Office personnel will automatically register participants separately to the translational components of the study (See Section 13).

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; Email: Random01@mayo.edu) to register all participants. 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 Intervention must take place at a CPN institution and under the supervision of a CPN clinician.

6.8.2.4 Pathology reports confirming diagnoses must be uploaded into the database via Medidata Rave ≤ 30 days post Registration.

6.8.2.5 Descriptive Factors collected at baseline:

- Participating Site
- Classic or attenuated FAP
- Baseline aspirin use
- Severity of duodenal polyposis (Spigelman stage 2 versus 3).

After the participant has been registered on to the study, values of the descriptive factors will be recorded.

6.9 Blinding and Unblinding Methods

Not applicable

6.10 Agent Destruction/Disposal

Per the agreement between NCI, DCP and Astellas Pharma for the supply of erlotinib, returned, unused, or undispensed study agent is to be returned to MRIGlobal.

Institutions that have policies requiring the immediate destruction of returned/unused erlotinib may do so under the following conditions: The site's process for destruction of patient returns should include documentation of the destruction that includes lot numbers and quantities. This documentation should then be provided to MRIGlobal (NCI.DCP@mriglobal.org). MRIGlobal will use the information to reconcile inventory.

At the completion of the study or upon expiration of the shelf supply, any undispensed study agent will be returned to MRIGlobal. They will reconcile and request permission for destruction from Astellas, per their requested procedure. Please following DCP Guidelines for agent returns and use the agent return from the DCP website.

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7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

Evaluation/ Procedure	Pre-Registration[1]	Screening/ Baseline[1]	Registration	Month 1 (+/- 4 days)	Months 2, 4, 5 (+/- 7 days)	Month 3 (+/- 7 days)	Month 6 or Early Termination (+/- 10 days)	Follow-Up – Month 7 (+/- 10 days)
Informed Consent	X							
Assess Eligibility		X						
Medical/Surgical History		X						
Physical Exam with vital signs (Ht, Wt, temp, pulse, BP)		X		X		X	X	
Alcohol and tobacco use assessments		X					X	
Clinical Laboratory Tests[2]		X		X		X	X[3]	X[3]
Urinalysis and urine cotinine[6]		X		X		X	X	
EGD/lower GI endoscopy with biopsies and tattooing		X[7]					X[7]	
Submission of CT imaging and report		X[4]					X[4]	
Research blood and urine collection		X				X	X	

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Evaluation/ Procedure	Pre-Registration[1]	Screening/ Baseline[1]	Registration	Month 1 (+/- 4 days)	Months 2, 4, 5 (+/- 7 days)	Month 3 (+/- 7 days)	Month 6 or Early Termination (+/- 10 days)	Follow-Up – Month 7 (+/- 10 days)
Pregnancy test, serum or urine, if applicable[5]		X	X			X	X	
Concomitant Medications		X		X	X	X	X	X
Dispense Study Agent and Medication Diaries			X			X		
Collect/Review Study Agent and Medication Diaries						X	X	
Was It Worth It (WIWI)							X	
Adverse Events			X	X	X	X	X	X
Telephone Contact					X			X

1. Pre-Registration and screening must take place ≤ 45 days prior to registration.
2. Clinical safety and toxicity laboratory testing includes CBC (with 5-part differential, platelets, and hemoglobin), Albumin, Bilirubin (Total), Calcium, Carbon dioxide (Bicarbonate), Chloride, Creatinine, Glucose, Alkaline phosphatase, Potassium, Protein (Total), Sodium, ALT/SGPT, AST/SGOT, and Blood Urea Nitrogen (BUN).
3. If any test results are outside of institutional limits of normal and clinically-significant, they will be repeated at Month 7.
4. For individuals with desmoid tumors who have CT imaging at least twice yearly as part of their standard clinical care/surveillance, CT images and local radiologists' reports will be submitted for central review ≤ 30 days from registration and ≤ 30 days after Month 6
5. A negative serum or urine pregnancy test (WOCBP only) must be documented ≤ 7 days prior to registration. If screening pregnancy test took place ≤ 7 days prior to registration, it does not have to be repeated.
6. Urine cotinine will be tested at baseline and Month 6/early termination only.
7. The lower GI endoscopy is preferred but it is optional. It should be performed only if clinically-indicated.

Samadder NJ, *et al. Gut* 2023; 72:256–263. doi: 10.1136/gutjnl-2021-326532

7.2 Baseline Testing/Prestudy Evaluation

Potentially eligible participants will undergo an educational session explaining the study, major endpoints, and potential risks. Based on the pre-registration inclusion and exclusion criteria (See Sections 4.1 and 4.2), participants will be determined to be potentially eligible for this trial. After appropriate discussions, written informed consent will be obtained. Results of clinically-indicated genetic analysis to confirm presence or absence of the APC mutation will be recorded, if available. Following informed consent, participants will be pre-registered to the study.

Screening will include a physical exam with vital signs, review of medical/surgical history, review of baseline symptoms and concomitant medications, alcohol and tobacco use assessments, clinical laboratory tests (CBC [with 5-part differential, platelets, and hemoglobin], Albumin, Bilirubin [Total], Calcium, Carbon dioxide [Bicarbonate], Chloride, Creatinine, Glucose, Alkaline phosphatase, Potassium, Protein [Total], Sodium, ALT/SGPT, AST/SGOT, and Blood Urea Nitrogen [BUN]), urinalysis and urine cotinine, and research blood and urine collection. A pregnancy test will be administered, if applicable.

If still eligible and willing, participants will undergo an esophagogastroduodenoscopy (EGD) plus lower GI endoscopy with biopsies and tattooing. The lower GI endoscopy is preferred but optional (See Section 7.6 for details).

For individuals with desmoid tumors who have CT imaging at least twice yearly as part of their standard clinical care, CT images along with the local radiologist's report from before and after intervention will be submitted for central review.

Screening must be completed ≤ 45 days prior to registration. After registration, participants will be dispensed a 3-month supply of study agent (See Section 5.2), a medication and symptom diary, and appropriate instructions.

7.3 Evaluation During Study Intervention

At Month 1 (+/-4 days), a visit will take place including physical exam with review of vital signs, review of adverse events and concomitant medications, clinical laboratory tests (CBC [with 5-part differential, platelets, and hemoglobin], Albumin, Bilirubin [Total], Calcium, Carbon dioxide [Bicarbonate], Chloride, Creatinine, Glucose, Alkaline phosphatase, Potassium, Protein [Total], Sodium, ALT/SGPT, AST/SGOT, and Blood Urea Nitrogen [BUN]), and urinalysis. The medication and symptom diaries will be reviewed to confirm participant understanding of the instructions, but they will not be collected.

Participants will be contacted by phone at Months 2, 4, and 5 (+/-7 days) to review adverse events and concomitant medications.

At Month 3 (+/-7 days), a visit will take place including physical exam with review of vital signs, review of adverse events and concomitant medications, clinical laboratory tests (CBC [with 5-part differential, platelets, and hemoglobin], Albumin, Bilirubin [Total], Calcium, Carbon dioxide [Bicarbonate], Chloride, Creatinine, Glucose, Alkaline phosphatase, Potassium, Protein [Total], Sodium, ALT/SGPT, AST/SGOT, and Blood Urea Nitrogen [BUN]), and urinalysis. Research blood and urine will be collected. A pregnancy test will be performed, if applicable. Any unused agent will be collected and a new supply (as described in Section 5.2) dispensed. Medication and symptoms diaries will be collected and new ones provided.

7.4 Evaluation at Completion of Study Intervention

At Month 6 (+/-10 days), a post-intervention visit will take place, including physical exam with review of vital signs, review of adverse events and concomitant medications, follow-up alcohol and tobacco use assessments, clinical laboratory tests (CBC [with 5-part differential, platelets, and hemoglobin], Albumin, Bilirubin [Total], Calcium, Carbon dioxide [Bicarbonate], Chloride, Creatinine, Glucose, Alkaline phosphatase, Potassium, Protein [Total], Sodium, ALT/SGPT, AST/SGOT, and Blood Urea Nitrogen [BUN]), urinalysis and urine cotinine, and research blood and urine collection. A pregnancy test will be performed, if applicable. Any unused agent and all medication/symptom diaries will be collected. Participants will undergo an EGD plus lower GI endoscopy with clearing of all polyps, according to institutional standards of care, plus research biopsies. All efforts should be made to confirm the same endoscopist performs the pre- and post-intervention endoscopy procedures.

7.5 Post-intervention Follow-up Period

Participants should be seen in the clinic or contacted by telephone to determine if any serious or non-serious adverse events have occurred within 30 days (±7 days) of termination of study participation, whether they complete the 6-month trial or not. If abnormal and clinically-significant laboratory values are found at the end of the study, these will be repeated at this time point. If all lab values are normal at Month 6, no additional laboratory tests will be done.

End-of-Treatment Evaluations due to early withdrawal

If a participant discontinues use of the study medication prior to 6-month trial completion, the following will be performed:

a. Reason for discontinuation will be determined and recorded in participant's file.
b. Clinic visit for history and physical exam, and EGD and lower GI endoscopy (if intact colon or rectal stump).
c. Management of adverse events according to institutional standards of good clinical practice and notification of NCI, DCP medical monitor
d. Review of concomitant medications, compliance assessment, and return of unused study agent
e. All blood tests and urinalysis/urine cotinine will be performed. Research blood and urine collection will be performed if consent provided.

7.6 Methods for Clinical Procedures

Endoscopic Screening: Participants will be monitored per institutional standards of good clinical practice (i.e. blood pressure, heart rate, pulse oxygenation) and then appropriately sedated. The examination and measurement components of the endoscopy procedures will be implemented in a manner consistent with the FAPEST study, recently reported in *JAMA,*[20] as outlined in brief below.

Upper GI Endoscopy: The duodenum will be evaluated by forward-viewing and/or side-viewing gastroscopes (with still and video documentation). Esophagogastroduodenoscopy (EGD) will be performed and a tattoo placed 10 cm distal to the duodenal bulb to define a region heretofore referred to as the *duodenal segment*, which will extend from the duodenal bulb distally to the tattoo. Endoscopic tattooing has been widely employed in previous research protocols and is clinically used by many authorities.[25, 26] Intramucosal injections of 0.5 ml to 2 ml are used as necessary to mark the mucosa. All

participants will have screening/baseline and final study endpoint (Month 6) UGI endoscopy as part of this trial.

Lower GI Endoscopy (preferred but optional): Willing participants will be evaluated via flexible proctosigmoidoscopy during the screening/baseline examination and final study endpoint (Month 6) evaluation. Flexible sigmoidoscopy will be used to examine the pouch, rectum (IRA), or rectal stump (IPAA) in FAP or attenuated FAP individuals who have undergone colectomy. For consistency, those with a rectum or rectal stump, biopsies of normal tissue will only be done if 10 cm of rectum (from the anal verge) is present.

Video Recording and capture of still images: All procedures will be recorded in high definition using Medicapture (or comparable) records to allow for blinded physician review as a secondary endpoint. Still images are highly recommended but not required. Still images (photos) should be taken at baseline and Month 6 in the center of the lumen at 1 cm increments during withdrawal from the duodenum. Any large polyps, particularly those that are biopsied for Spigelman staging at baseline, should also be photographed with the biopsy forceps visible to provide a reference for size.

Pre-treatment Endoscopic Assessment. Topical lidocaine will be used for pharyngeal anesthesia. Conscious sedation will be administered by the endoscopist-investigator, as is the current clinical standard of practice. Medicines will primarily consist of midazolam and fentanyl, but other sedatives are occasionally needed. Endoscopy will be performed in the standard fashion. A side-viewing endoscope (preferred) will be used specifically to examine and record the size of the ampulla of Vater in the duodenum. If this cannot be done, then viewing with the forward viewing endoscope is acceptable. Biopsies of the ampulla of Vater will only be obtained if it appears abnormally large or suspicious for malignancy. The size, location, and number of polyps will be determined and recorded, consistent with procedures that have been used extensively in polyp studies. Each polyp in the duodenal segment will be measured, mapped, and recorded at 1-cm intervals in the 10-cm segment. In the rectum, each polyp will be measured and recorded.

Counting and mapping polyps will be performed prior to collection of any biopsies or removal of any polyps.

At baseline, at least one polyp will be biopsied and sent for local histological analysis for eligibility determination and Spigelman stage determination. This specimen will be collected and processed according to institutional standard operating procedures. Any lesions containing high-grade dysplasia or cancer will result in a referral to surgery and oncology, and, exclusion of the patient from the study. Any lesions that are ≥ 10mm and/or worrisome for high grade dysplasia or cancer in the opinion of the endoscopist, should be removed or sampled according to institution standards of care. This should be noted on the endoscopy report. Participants with extensive, but quantifiable, duodenal polyposis will not be necessarily excluded from the study unless histological analysis reveals high grade dysplasia or cancer. These specimens are not among the specimens being collected for research purposes.

For research purposes, four endoscopic biopsies of grossly normal duodenal mucosa and one (for Spigelman 2) or two (Spigelman 3) endoscopic biops(ies) of duodenal polyp will be obtained from all participants at screening/baseline and end of the study (Month 6). One biopsy from both normal and polyp at each time point will be placed in RNA later, and the remaining specimens will be snap frozen in liquid nitrogen. Note: if Spigelman Stage is not known at the time of the baseline endoscopy, the

endoscopists should use their best clinical judgement regarding Spigelman 2 versus Spigelman 3 based on the size and number of polyps. If the subsequent pathology assessment differs from the endoscopist's assessment, a note-to-file will be created for the participant's file.

Polyps on the ampula of Vater should be included in the mapping and counting process. These polyps should be biopsied if worrisome.

At Month 6, the side-viewing endoscope (preferred) will be used specifically to examine and record the size of the ampulla of Vater in the duodenum. If this cannot be done, then viewing with the forward viewing endoscope is acceptable.

If there are at least 10 cm of rectum, four endoscopic biopsies of normal rectal mucosa will be obtained in patients with a rectal stump or intact rectum at screening/baseline and end of the study (Month 6). One biopsy of rectal mucosa at each time point will be placed in RNA later, and the remaining specimens will be flash frozen in liquid nitrogen.

For individuals with desmoid tumors who have surveillance CT (with contrast) imaging at least twice yearly as part of their standard clinical care, CT images along with the local radiologist's report will be submitted for central radiology review, which will take place at the University of Utah. The radiology reviewer (MEH) will be blinded as to the time point (pre-intervention versus post-intervention) and enrolling institution.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Primary Endpoints

- Polyp Burden: To assess the mean percent change in duodenal polyp burden (sum of diameters from all polyps) from baseline to 6 months post-intervention as assessed by esophagogastroduodenoscopy (EGD) for FAP subjects receiving weekly erlotinib. The hypothesis is that weekly erlotinib will significantly reduce duodenal polyp burden after 6 months of treatment.
- Adverse events (if polyp burden shows a significant decrease from baseline): To assess the grade 2/3 adverse event rate in this population and compare it to historical data. The hypothesis is that weekly erlotinib will significantly reduce the grade 2/3 AE rate compared to historical control data.

8.2 Secondary Endpoints

- To evaluate all adverse events associated with the weekly erlotinib;
- To assess the absolute and percent change in duodenal polyp number from baseline to 6 months;
- To assess the absolute and percent changes in lower gastrointestinal polyp burden and number for the subset of participants with ileal pouch anal anastomosis (IPAA) or ileo-rectal anastomosis with rectal stump (anticipated to be approximately 70% of registered cohort); and
- To assess the absolute and percent change in desmoid tumor size in participants who have baseline and follow up CTs performed as part of their standard of care (anticipated to be approximately 30% of the registered cohort);

- Gene expression profiles in duodenal adenomas and uninvolved tissue will be compared between baseline and endpoint samples using negative binomial statistics (DESeq2):
    - Identify differentially expressed genes between duodenal polyps and uninvolved tissue at endpoint compared to baseline;
    - Evaluate the effect of weekly erlotinib on EGFR and Wnt target gene expression in duodenal adenomas
    - Evaluate the effect of weekly erlotinib on immune response signaling in duodenal adenomas and uninvolved tissue. Global gene expression (RNA transcriptome) will be measured by RNA sequencing. This global RNA analysis includes all immune response genes. These analyses will be done by Dr. Don Decker, Huntsman Cancer Institute, University of Utah.

8.3 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 8.4), major treatment violation (see Section 8.4) 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 described below (if participant does not refuse, is not lost to follow-up, or unless it is clinically contraindicated).

If a participant discontinues study agent before Month 3 due to adverse events, it is preferable to continue AE assessment through Month 7. This can be done by phone, if preferred. Endoscopies and blood testing do not need to be performed unless clinically indicated.

If the participant discontinues study agent after the Month 3 time point, perform the Month 6 visit, including endoscopy, within 10 days of discontinuing agent. If it cannot be done within 10 days, schedule the visit and procedures as close as possible to this time point.

See Section 8.4 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-registration were severely violated).

8.4 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.

8.5 Study Termination

NCI, DCP as the study sponsor has the right to discontinue the study at any time.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Rationale for Methodology Selection

See Biomarker Methods Development Report.

9.2 Comparable Methods

Methodology for this study is consistent with the FAPEST trial,[20] which should result in data that can be compared to existing data.

10. SPECIMEN MANAGEMENT

10.1 Laboratories

Clinical laboratory evaluations will take place at each institution's clinical laboratories as listed on the study-specific FDA form 1572. These include blood chemistry, hematology, and urinalyses.

RNA extractions and RNA sequencing:
Don A. Delker, Ph.D., Laboratory Manager
Division of Gastroenterology, Hepatology and Nutrition

School of Medicine, University of Utah
30 North 1900 East, Salt Lake City, UT 84132
Phone: 801-585-0328
Email: don.delker@hsc.utah.edu

10.2 Collection and Handling Procedures

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

- **All sections of the requisition form, specimen submission CRFs, and specimen collection labels must be completed and legible.**
- **Specimens should be sent overnight via FedEx® on dry ice. All specimens must be shipped to the address provided on the specimen shippers.**
- **All specimens will be shipped in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations.**

10.2.1 Clinical Blood and Urine Specimens

Clinical blood and urine specimens will be collected and processed according to each institution's internal standard operating procedures. Results will be reported on the appropriate case report forms.

10.2.2 Research Blood and Urine Specimens

Using the required BAP kits, an optional blood specimen (one 10 mL no additive red-topped tube, and one 10 mL purple topped tube) will be collected at screening/baseline and end of study (Month 6), processed into serum, plasma, and buffy coat, frozen, and shipped to BAP (see below) for storage for future research.

An optional urine specimen will also be collected, frozen, and shipped on dry ice, overnight to the BAP freezer.

Specimens will be frozen at -20^{o} or colder and shipped on dry ice, M-F, overnight to the BAP Freezer:

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

Questions should be addressed to:
Roxann Neumann, Biospecimens Resource Manager
Phone: 507-538-0602; Email: Neumann.roxann@mayo.edu

10.2.3 Tissue Specimen Collection and Submission

At baseline, at least one polyp will be removed and sent for local histological analysis for eligibility determination and Spigelman stage determination (See Section 7.6). This specimen will be collected and processed according to institutional standard operating procedures.

Four endoscopic biopsies of normal duodenal mucosa and one (for Spigelman 2) or two (Spigelman 3) endoscopic biops(ies) of duodenal polyp will be obtained from all participants at screening/baseline and end of the study (Month 6). One biopsy from both normal and polyp at each time point will be placed in RNA later, and the remaining specimens will be snap frozen in liquid nitrogen.

Four endoscopic biopsies of normal rectal mucosa will be obtained in patients with a rectal stump or intact rectum at screening/baseline and end of the study (Month 6). One biopsy of rectal mucosa at each time will be placed in RNA later, and the remaining specimens will be flash frozen in liquid nitrogen.

MAY2016-07-01
Version 3.0, Amendment 8
July 22, 2019

Research Specimen Summary

Specimen	Time Point(s)	Processing	Shipping
Optional research blood: one 10 mL EDTA lavender - topped and one 10 mL red-topped tube	Baseline/screening, Month 3, and Month 6	Utilize BAP kits; Process into red-top tube into serum at site. Process lavender-topped tube into plasma and buffy coat at site. Freeze all specimens. Place sample type on the label: P=plasma; B-Buffy; S=Serum	Ship to BAP FedEx™ overnight, M-F, on dry ice. BAP will accession and store at -80°C.
Optional research blood: Two 10 mL EDTA lavender-topped tube	Baseline/screening, Month 3, and Month 6	Utilize BAP kit. Centrifuge, aliquot into intermediate tube, and centrifuge again to produce platelet poor plasma (PPP) per institutional lab procedures. Be sure to not disturb the residual blood cells carried over from the first centrifugation step when aliquoting PPP. See BAP kit instructions for details. Freeze.	Ship to BAP FedEx™ overnight, M-F, on dry ice. BAP will accession and store at -80°C.
Optional urine specimen	Baseline/screening, Month 3 and Month 6	Utilize BAP kit; aliquot from collection container to tubes provided. Freeze.	Ship to BAP FedEx™ overnight, M-F, on dry ice. BAP will accession and store at -80°C.
Tissue if Spigelman 2:	Baseline/screening and Month 6	1. Four biopsies of normal duodenal mucosa and <u>one</u> biopsy of duodenal polyp. 2. Place one normal duodenal mucosa biopsy and one polyp in RNAlater. Refrigerate at 4-6°C or snap freeze. 3. Snap freeze remaining three specimens in separate cryovials in liquid nitrogen. 4. Make sure labels distinguish normal duodenal mucosa versus polyp specimens.	Ship frozen specimens to BAP FedEx™ overnight, M-F, on dry ice. Ship specimen in RNALater to BAP on a cold pack (or dry ice if frozen). Accession. Store specimens at -80°C until requested.
Tissue if Spigelman 3:	Baseline/screening and Month 6	1. Four biopsies of normal duodenal mucosa and <u>two</u> biopsies of duodenal polyps. 2. Place one normal duodenal mucosa biopsy and one polyp in RNAlater. Refrigerate at 4-6°C or snap freeze 3. Snap freeze all remaining specimens in separate cryovials in liquid nitrogen (three normal duodenal mucosa and one polyp). 4. Make sure labels distinguish normal duodenal mucosa versus polyp specimens.	Ship frozen specimens to BAP FedEx™ overnight, M-F, on dry ice. Ship specimens in RNALater to BAP FedEx™ overnight, M-F, on a cold pack (or dry ice if frozen). Accession. Store specimens at -80°C until requested.
Tissue if a rectal stump or intact rectum:	Baseline/screening and Month 6	1. Four biopsies of normal rectal mucosa 2. Place one rectal mucosa biopsy in RNAlater and refrigerate at 4-6°C or snap freeze 3. Snap freeze the three remaining rectal biopsies in liquid nitrogen.	Ship frozen specimens to BAP FedEx™ BAP FedEx™ overnight, M-F, on dry ice. Ship specimens in RNALater to BAP FedEx™ overnight, M-F, on a cold pack (or dry ice if frozen). Accession. Store specimens at -80°C until requested.

Samadder NJ, *et al. Gut* 2023; 72:256–263. doi: 10.1136/gutjnl-2021-326532

10.3 Labeling and 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 specimens must be labeled with the study number, participant ID, participant initials (if allowed per institutional policy), type of specimen (normal mucosa versus polyp), source of specimen (duodenum versus rectum), additive (RNALater versus none/snap frozen), date and time of collection. Abbreviations are allowed, if legible (see kit requisition form or instructions).

Example:
MAY2016-07-01
Month 6
CPN00023
T O M
mm/dd/2016, 14:30
Duodenal polyp
RNAlater

All sections of the requisition form and specimen collection labels must be completed and legible. Specimen collection vial labels should match the requisition form exactly.

All specimens should be sent over night (Monday through Friday) via FedEx® on dry ice or on a cold pack (See Research Specimen Summary Table, Section 10.2). Site staff will send an email with FedEx tracking number to the Biospecimen Resource Manager so arrangements can be made to receive the specimens and place immediately in appropriate storage facilities. Exceptions for holidays will be communicated in advance to participating organizations. All specimens must be shipped to the address provided on the specimen shippers and listed above (See Section 10.2).

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-F) for storage (until request is received to transfer to DCP Biospecimens Repository) to:

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

At study completion, 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 can be found in §6.2 Reported Adverse Events and Potential Risks, 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 AE reporting.

- AE verbatim term
- NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) AE term (MedDRA lowest level term)
- CTCAE (MedDRA) System Organ Class (SOC)
- Event onset date and event ended date
- Treatment assignment code (TAC) at time of AE onset
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a 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 CTCAE version 4.0. The CTCAE provides descriptive terminology (MedDRA lowest level term) and a grading scale for each AE 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 grade associated with the CTCAE 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 AE is related to study agent will be classified as one of the following: not related, unlikely, possible, probable, or definite.

11.1.5 Follow-up of AEs

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such.

11.2 Serious Adverse Events

11.2.1 DEFINITION: Regulations at 21 CFR §312.32 (revised April 1, 2014) defines an SAE as any untoward medical occurrence that at any dose has one or more of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to perform normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization should also be considered serious when, based upon

appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes.

11.2.2 Reporting SAEs to DCP

11.2.2.1 The Lead Organization and all Participating Organizations will report SAEs following the current, active DCP SAE reporting SOP available at this location: http://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools/2012-consortia.

11.2.2.2 Contact the DCP Medical Monitor by phone 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

Guidance for the process of coding the SAE can be obtained by contacting the NCI MD Help Desk: adeersmd@tech-res.com

11.2.2.3 The Lead Organization and all Participating Organizations will submit SAE reports, following the current, active DCP SAE reporting SOP within 48 hours of learning of the event:

1. **DCP Medical Monitor: dellazannagj@mail.nih.gov**
2. **DCP's Regulatory Contractor CCS Associates, Inc.: safety@ccsainc.com**
3. **CPN Operations Office: cancerpreventionnetwork@mayo.edu**

Follow up information should also be sent to all of the above.

11.2.2.4 The DCP Medical Monitor and CCSA regulatory and safety staff will determine which SAEs require FDA submission as IND safety reports.

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

11.2.3 Follow-up of SAE

Site staff should send follow-up reports as requested when additional information is available. Follow-up information should be submitted to DCP as soon as available. SAEs will be treated according to institutional standards of good clinical practice and followed to resolution.

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
- Endoscopy 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 and requisition forms (signed and dated).

12.4 Data and Safety Monitoring Plan

The CPN Master DSMP is applicable to all studies within the CPN Consortium and 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 (along with the study Medical Monitor) 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 single arm Phase II trial designed to assess the effect of weekly erlotinib among FAP subjects. The primary objective of this trial is to assess the mean percent change in duodenal polyp burden (sum of diameters from all polyps) from baseline to 6 months post-intervention for FAP subjects receiving weekly erlotinib. The hypothesis is that weekly erlotinib will significantly reduce duodenal polyp burden after 6 months of treatment. If a significant reduction in polyp burden is shown after 6 months of treatment, we will also assess the grade 2/3 adverse event rate in this population and compare it to historical data. The hypothesis is that weekly erlotinib will significantly reduce the grade 2/3 AE rate

compared to historical control data. Statistical considerations regarding sample size and study power are based on this primary study objective. Secondary endpoints will evaluate all adverse events, assess the absolute and percent change in duodenal polyp number from baseline to 6 months, and assess the absolute and percent changes in lower gastrointestinal polyp burden and number within patient subsets of interest.

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

There will be no randomization or stratification for this study. This study will be a single arm Phase II trial, where all subjects will be accrued in one stage.

13.3 Accrual and Feasibility

The study design requires a total of up to 70 participants for screening evaluation with approximately 60 moving forward to registration and intervention due to anticipated screen failures of approximately 15%. We further expect up to 15% of participants to drop out or otherwise become non-evaluable by 6 months such that approximately 50 subjects should be evaluable for the primary endpoint. We expect to enroll an average of 1 participant per month for each of the participating CPN sites, for an overall registration rate of approximately 6 participants per month. With this accrual rate and with a 6 month ramp up for participating organizations, we plan to complete accrual in about 18 months, which includes 2 months for planned slowing of enrollment due to holidays, etc. Accounting for patient follow-up, data entry, and analysis, the study should be completed within approximately 2.5 years.

Planned Accrual Estimates

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	Total
American Indian/Alaska Native	**0**	**0**	**0**	**0**	**0**
Asian	**0**	**1**	**0**	**0**	**1**
Native Hawaiian or Other Pacific Islander	**0**	**0**	**0**	**0**	**0**
Black or African American	**4**	**5**	**1**	**1**	**11**
White	**14**	**15**	**7**	**10**	**46**
More Than One Race	**0**	**1**	**0**	**1**	**2**
Total	**18**	**22**	**8**	**12**	**60**

Racial Categories	INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native					
Asian					
Native Hawaiian or Other Pacific Islander					
Black or African American					
White					
More Than One Race					
Total					**0**

13.4 Primary Objective, Endpoint(s), Analysis Plan

The primary objective of this trial is to assess the mean percent change in duodenal polyp burden (sum of diameters from all polyps) from baseline to 6 months post-intervention for FAP subjects receiving weekly erlotinib. The hypothesis is that weekly erlotinib will significantly reduce duodenal polyp burden after 6 months of treatment. If a significant reduction in polyp burden is shown after 6 months of treatment, we will also assess the grade 2/3 adverse event rate in this population and compare it to historical data. The hypothesis is that weekly erlotinib will significantly reduce the grade 2/3 AE rate compared to historical control data. The study design below assesses the co-primary endpoints using a hierarchical testing strategy, where the AE primary endpoint will only be assessed if Polyp Burden is significantly reduced. With this design strategy, we're able to maintain alpha = 0.05 for each primary endpoint.

Polyp Burden Primary Endpoint: Based on the prior data from the FAPEST study, the sulindac/erlotinib arm had a 8.5-mm (38%) median decrease (38% decrease for mean as well) in polyp burden compared to a median increase of 8 mm (31%) in the placebo arm (44% mean increase). This difference was highly significant ($p<0.001$).[20]

With 50 evaluable subjects, we would have 93% power to detect a significant mean percentage decrease in polyp burden from baseline of 15% for erlotinib weekly schedule, with 2-sided significance level of 0.05 (1 sample paired t-test). This assumes an effect size of 50% and a standard deviation (SD) of 30%. Basically, we could detect ½ a SD for this test, so if the SD ends up being 20%, we could detect a reduction of 10% or more in polyp burden. For this test, we will assume the user-specified null hypothesis is 0%, so that we're testing any significant reduction in polyp burden from baseline to 6 months. If for some reason, the sample size doesn't meet target accrual of 50 evaluable subjects, here are some other possibilities for the same effect size and alpha. With at least 34 eligible patients, we'd have at least 80% power for the polyp burden primary endpoint. With at least 35 eligible patients, we'd have at least 80% power for both primary endpoints (polyp burden and AEs), just in case the accrual suffers and we need to stop the trial early.

Number Eligible	Power
34	80%
35	81%
40	86%
44	90%

AE Primary Endpoint (only tested if Polyp Burden is significantly reduced, otherwise not important): The combination arm (sulindac and erlotinib daily) from the FAPEST study, showed much higher rates of grade 2/3 AEs (at least possibly related) compared to placebo (46% vs. 13%). It also showed much higher rates of Rash for both grade 1-3 (87%) and grade 2-3 (26%) as compared to placebo (20% for grade 1-3 and 0% for grade 2-3).[20] Since this study will be testing erlotinib weekly we hypothesize that the AE rates will be significantly lower than found in the aforementioned Samadder study.

With 50 evaluable subjects, we would have 94% power to detect a reduction in grade 2/3 AE rate from 50% to 25%, assuming a 2-sided significance level of 0.05. This is based on an Exact test for a single proportion, assuming 50% as the user specified null hypothesis. If for some reason, the sample size doesn't meet target accrual of 50 evaluable subjects, here are some other possibilities for the same effect size and alpha. All eligible participants who start treatment will be evaluable for the AE primary endpoint.

With 44 eligible patients, we'd still have 93% power as well for this AE primary endpoint. With 40 eligible, we'd have 89% power, and with 35 eligible we'd have 83% power. With at least 35 eligible patients, we'd have at least 80% power for both primary endpoints, just in case the accrual suffers and we need to stop the trial early.

Number Eligible	Power
34	78%
35	83%
40	89%
44	93%

13.5 Secondary Objectives, Endpoints, Analysis Plans

- To evaluate all adverse events associated with the weekly erlotinib;
- To assess the absolute and percent change in duodenal polyp number from baseline to 6 months;
- To assess the absolute and percent changes in lower gastrointestinal polyp burden and number for the subset of participants with ileal pouch anal anastomosis (IPAA) or ileo-rectal anastomosis with rectal stump (anticipated to be approximately 70% of registered cohort); and
- To assess the absolute and percent change in desmoid tumor size in participants who have baseline and follow up CTs performed as part of their standard of care (anticipated to be approximately 30% of the registered cohort);
- Gene expression profiles in duodenal adenomas and uninvolved tissue will be compared between baseline and endpoint samples using negative binomial statistics (DESeq2):

- Identify differentially expressed genes between duodenal polyps and uninvolved tissue at endpoint compared to baseline;
- Evaluate the effect of weekly erlotinib on EGFR and Wnt target gene expression in duodenal adenomas;
- Evaluate the effect of weekly erlotinib on immune response signaling in duodenal adenomas and uninvolved tissue.

The hypothesis is that weekly erlotinib treatment will reduce the number of differentially expressed genes and EGFR signaling in duodenal adenomas similar to findings from the previous erlotinib + sulindac study. We also anticipate Wnt signaling will be inhibited in duodenal polyps from patients on drug. Using Ingenuity pathway analysis (IPA, Qiagen) we will evaluate the effect of erlotinib on immune response signaling pathways (IFNG, IL12) previously observed to be enhanced in patients receiving erlotinib + sulindac.

13.6 Reporting and Exclusions

All registered participants who start treatment and complete both the baseline and 6-month post-baseline evaluation will be evaluable for the polyp burden primary endpoint of this study using the modified intent-to-treat principle. We plan to over register by about 15% to ensure an adequate sample size in the primary analysis cohort. 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. All eligible participants who start treatment will be evaluable for the AE primary endpoint.

13.7 Evaluation of Toxicity (Secondary endpoint)

All registered and treated participants will be evaluable for adverse events (AEs) from the time of their first dose of weekly erlotinib treatment. To evaluate the AE profile for this treatment, 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 2+ 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 Adverse Event Stopping Rule

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) using the adverse event (AE) stopping rule specified below.

Adverse Event Stopping Rule: The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of

either (1) the study re-opening to accrual after any temporary suspension or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team in consultation with the Mayo DSMB may also choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy any of the following criteria:

- If, at any time, two of the initial 20 treated participants or 10% of all participants, i.e. when accrual is greater than 20 participants, have experienced a Grade 4 adverse event
- If, at any time, a Grade 5 event occurs that is at least possibly related to treatment
- In addition, each Grade 5 event, regardless of attribution, will be reviewed on a case-by-case basis in a real-time fashion to determine whether or not study accrual should be suspended. We also will 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

All registered participants who start treatment and complete both the baseline and 6-month post-baseline evaluation will be evaluable for the polyp burden primary endpoint of this study using the modified intent-to-treat principle. All conclusions regarding efficacy will be based on all participants who completed both the baseline and 6-month post-baseline evaluations. Sub-analyses 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 may not serve as the basis for drawing conclusions concerning efficacy, and the reasons for excluding participants from the analysis should be clearly reported. For all measurements of response (i.e. the polyp burden primary endpoint), the 95% confidence intervals will also be provided. All eligible patients who start treatment will be evaluable for the AE primary endpoint.

13.9 Interim Analysis

Not applicable for this study.

13.10 Ancillary Studies

Laboratory measures will be correlated with participant outcomes (i.e., polyp burden, adverse events) and with each other as well. Cut-points will be determined based on previously defined and accepted standards. Descriptive statistics and simple scatter plots will be generated to review the tissue-based biomarker data. For continuous variables, the actual and % change in the level of each of the biomarkers from pre- to post-intervention will be explored using Wilcoxon signed rank tests, and paired sample t-tests. All categorical variables will be analyzed using chi-square tests or Fisher's exact test. For all translational endpoints, any notable statistical result will be viewed as an impetus for further study rather than as a definitive finding in and of itself.

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 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 Good Clinical Practice 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 Central 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 CIRB. 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. Subjects 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 specimens, 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 DCP's Regulatory Contractor:

Paper Document/CD-ROM Submissions:
Regulatory Affairs Department
CCS Associates, Inc.
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 DCP's 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 participants and/or their insurance carriers. This does not include costs of tests and procedures that are a part of the participant's normal clinical care. This also 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.

REFERENCES

1. Giardiello FM, Hamilton SR, Krush AJ, Piantadosi S, Hylind LM, Celano P, Booker SV, Robinson CR, Offerhaus GJ. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. The New England journal of medicine 1993;328:1313-6.
2. Giardiello FM, Yang VW, Hylind LM, Krush AJ, Petersen GM, Trimbath JD, Piantadosi S, Garrett E, Geiman DE, Hubbard W, Offerhaus GJ, Hamilton SR. Primary chemoprevention of familial adenomatous polyposis with sulindac. The New England journal of medicine 2002;346:1054-9.
3. Debinski HS, Trojan J, Nugent KP, Spigelman AD, Phillips RK. Effect of sulindac on small polyps in familial adenomatous polyposis. Lancet 1995;345:855-6.
4. Nugent KP, Farmer KC, Spigelman AD, Williams CB, Phillips RK. Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis. The British journal of surgery 1993;80:1618-9.
5. Phillips RK, Wallace MH, Lynch PM, Hawk E, Gordon GB, Saunders BP, Wakabayashi N, Shen Y, Zimmerman S, Godio L, Rodrigues-Bigas M, Su LK, Sherman J, Kelloff G, Levin B, Steinbach G. A randomised, double blind, placebo controlled study of celecoxib, a selective cyclooxygenase 2 inhibitor, on duodenal polyposis in familial adenomatous polyposis. Gut 2002;50:857-60.
6. Arber N, Eagle CJ, Spicak J, Racz I, Dite P, Hajer J, Zavoral M, Lechuga MJ, Gerletti P, Tang J, Rosenstein RB, Macdonald K, Bhadra P, Fowler R, Wittes J, Zauber AG, Solomon SD, Levin B. Celecoxib for the prevention of colorectal adenomatous polyps. The New England journal of medicine 2006;355:885-95.
7. Steinbach G, Lynch PM, Phillips RK, Wallace MH, Hawk E, Gordon GB, Wakabayashi N, Saunders B, Shen Y, Fujimura T, Su LK, Levin B, Godio L, Patterson S, Rodriguez-Bigas MA, Jester SL, King KL, Schumacher M, Abbruzzese J, DuBois RN, Hittelman WN, Zimmerman S, Sherman JW, Kelloff G. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. The New England journal of medicine 2000;342:1946-52.
8. M N. Pfizer, Inc.; Withdrawal of Approval of Familial Adenomatous Polyposis Indication for CELEBREX. In: Register OotF, ed. Volume 2015. New York, NY: P, 2012.
9. Coffey RJ, Hawkey CJ, Damstrup L, Graves-Deal R, Daniel VC, Dempsey PJ, Chinery R, Kirkland SC, DuBois RN, Jetton TL, Morrow JD. Epidermal growth factor receptor activation induces nuclear targeting of cyclooxygenase-2, basolateral release of prostaglandins, and mitogenesis in polarizing colon cancer cells. Proceedings of the National Academy of Sciences of the United States of America 1997;94:657-62.
10. Eisinger AL, Nadauld LD, Shelton DN, Peterson PW, Phelps RA, Chidester S, Stafforini DM, Prescott SM, Jones DA. The adenomatous polyposis coli tumor suppressor gene regulates expression of cyclooxygenase-2 by a mechanism that involves retinoic acid. The Journal of biological chemistry 2006;281:20474-82.
11. Roberts RB, Min L, Washington MK, Olsen SJ, Settle SH, Coffey RJ, Threadgill DW. Importance of

epidermal growth factor receptor signaling in establishment of adenomas and maintenance of carcinomas during intestinal tumorigenesis. Proceedings of the National Academy of Sciences of the United States of America 2002;99:1521-6.

12. Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. Gastroenterology 2010;138:2044-58.
13. Biasco G, Pantaleo MA, Di Febo G, Calabrese C, Brandi G, Bulow S. Risk of duodenal cancer in patients with familial adenomatous polyposis. Gut 2004;53:1547; author reply 1547.
14. Bulow S, Bjork J, Christensen IJ, Fausa O, Jarvinen H, Moesgaard F, Vasen HF. Duodenal adenomatosis in familial adenomatous polyposis. Gut 2004;53:381-6.
15. Offerhaus GJ, Giardiello FM, Krush AJ, Booker SV, Tersmette AC, Kelley NC, Hamilton SR. The risk of upper gastrointestinal cancer in familial adenomatous polyposis. Gastroenterology 1992;102:1980-2.
16. Jagelman DG, DeCosse JJ, Bussey HJ. Upper gastrointestinal cancer in familial adenomatous polyposis. Lancet 1988;1:1149-51.
17. Vasen HF, Bulow S, Myrhoj T, Mathus-Vliegen L, Griffioen G, Buskens E, Taal BG, Nagengast F, Slors JF, de Ruiter P. Decision analysis in the management of duodenal adenomatosis in familial adenomatous polyposis. Gut 1997;40:716-9.
18. Heiskanen I, Kellokumpu I, Jarvinen H. Management of duodenal adenomas in 98 patients with familial adenomatous polyposis. Endoscopy 1999;31:412-6.
19. Conio M, Gostout CJ. Management of duodenal adenomas in 98 patients with familial adenomatous polyposis. Gastrointestinal endoscopy 2001;53:265-6.
20. Samadder NJ, Neklason DW, Boucher KM, Byrne KR, Kanth P, Samowitz W, Jones D, Tavtigian SV, Done MW, Berry T, Jasperson K, Pappas L, Smith L, Sample D, Davis R, Topham MK, Lynch P, Strait E, McKinnon W, Burt RW, Kuwada SK. Effect of Sulindac and Erlotinib vs Placebo on Duodenal Neoplasia in Familial Adenomatous Polyposis: A Randomized Clinical Trial. JAMA 2016;315:1266-75.
21. Saba NF, Hurwitz SJ, Kono SA, Yang CS, Zhao Y, Chen Z, Sica G, Muller S, Moreno-Williams R, Lewis M, Grist W, Chen AY, Moore CE, Owonikoko TK, Ramalingam S, Beitler JJ, Nannapaneni S, Shin HJ, Grandis JR, Khuri FR, Chen ZG, Shin DM. Chemoprevention of head and neck cancer with celecoxib and erlotinib: results of a phase ib and pharmacokinetic study. Cancer prevention research 2014;7:283-91.
22. Lubet RA, Szabo E, Iwata KK, Gill SC, Tucker C, Bode A, Steele VE, Juliana MM, Nicastro HL, Grubbs CJ. Effect of intermittent dosing regimens of erlotinib on methylnitrosourea-induced mammary carcinogenesis. Cancer prevention research 2013;6:448-54.
23. Milton DT, Azzoli CG, Heelan RT, Venkatraman E, Gomez JE, Kris MG, Krug LM, Pao W, Rizvi NA, Dunne M, Miller VA. A phase I/II study of weekly high-dose erlotinib in previously treated patients with nonsmall cell lung cancer. Cancer 2006;107:1034-41.
24. Grommes C, Oxnard GR, Kris MG, Miller VA, Pao W, Holodny AI, Clarke JL, Lassman AB. "Pulsatile" high-dose weekly erlotinib for CNS metastases from EGFR mutant non-small cell lung cancer. Neuro-oncology 2011;13:1364-9.
25. Hyman N, Waye JD. Endoscopic four quadrant tattoo for the identification of colonic lesions at surgery. Gastrointestinal endoscopy 1991;37:56-8.
26. Shatz BA, Thavorides V. Colonic tattoo for follow-up of endoscopic sessile polypectomy. Gastrointestinal endoscopy 1991;37:59-60.

MAY2016-07-01
Version 3.0, Amendment 8
July 22, 2019

Summary of Changes – Informed Consent Form

NCI Protocol #: MAY2016-07-01
Local Protocol #: MAY2016-07-01
Protocol Version Date: July 22, 2019

Protocol Title: Phase II Trial of Weekly Erlotinib Dosing to Reduce Duodenal Polyp Burden Associated with Familial Adenomatous Polyposis

Informed Consent Version Date: July 22, 2019

Please note that the page numbers in the table below refer to the Word version of the Informed Consent Form that will be submitted to the CIRB.

There are no changes in the informed consent template other than the version number and date.

MAY2016-07-01
Version 3.0, Amendment 8
July 22, 2019

NCI, DCP CONSENT FORM TEMPLATE FOR CONSORTIA CANCER CHEMOPREVENTION TRIALS

Study Title for Study Participants: Testing Weekly Erlotinib for Familial Adenomatous Polyposis (FAP)

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Phase II Trial of Weekly Erlotinib Dosing to Reduce Duodenal Polyp Burden Associated with Familial Adenomatous Polyposis

Introduction

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part in the research. Please take your time to make your decision about volunteering. You may discuss your decision with your friends and family. You can also discuss this study with your health care team. If you have any questions, you can ask your study doctor for more of an explanation. You should only agree to participate in this study when you are comfortable enough with the information so that you can make an informed decision about joining.

What is the usual approach to my Familial Adenomatous Polyposis (FAP)?

You are being asked to take part in this study because you have FAP and are at increased risk for developing colon cancer. People who are at increased risk and choose not to participate in a study are usually followed closely by their doctor, with regular examinations of their colon, rectum, and small bowel to watch for the development of polyps and cancer.

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

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

- you may choose to have the usual approach described above,
- 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®) taken once per week and find out what effects, if any, erlotinib has on people and their risk of colon cancer. There will be about 60 people taking part in this study.

Erlotinib (Tarceva®) is a targeted cancer therapy drug that interferes with the growth and spread of cancer cells in the body. Targeted cancer therapies "target" cancer cells while doing little damage to normal cells. Erlotinib has been effective in treating many different kinds of cancer, including lung and pancreatic cancer, and is approved by the FDA for targeted cancer therapy. It is not approved for cancer prevention.

Several recent studies have shown that erlotinib may also be effective in reducing the number of polyps and increasing the time to reappearance of polyps. This study will test a weekly dose of erlotinib, instead of a daily dose, to see if it works just as well with fewer worrisome side effects. Because Erlotinib has not been approved for reduction of polyps, using it for this study is experimental.

Everyone participating in the study will be given the same dose of erlotinib, which will be 350 mg (two 150 mg tablets plus two 25 mg tablets) once every week for 6 months.

How long will I be in this study?

You will be on the study for up to 8 months. After signing this informed consent document, you will have several tests to find out if you can take the study drug. This may take up to 28 days before you begin taking the study drug. You will receive the study drug for 6 months. Even if you do not finish the study, your doctor will continue to watch you for side effects and follow your condition for one additional month.

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

Before you begin the study:
You will sign this document, and you will be "pre-registered" and assigned your unique participant identification (PID) number. From that point forward, all of your information and specimens will be identified only with this number. Some of the exams, tests, and procedures you will have are part of the usual approach for your condition. However, there are some extra examinations, blood tests, and procedures that you will need to have if you take part in this study.

You will need to have the following extra evaluations and procedures to find out if you can be in the study:

- We will review your medical and surgical history.
- We will review of any medications you are taking and any symptoms you are experiencing.
- Blood and urine will be collected for tests to check your health and how well your organs function.
- Assessment of your alcohol and tobacco use
- **Optional:** Blood and urine will be collected for research.

- A pregnancy test will be performed within 7 days prior to registration if you are capable of having children.
- Esophagogastroduodenoscopy (EGD) and lower gastrointestinal endoscopy procedures will be performed to look at your digestive system and evaluate any polyps that are present
- Biopsies of your digestive tract will be collected for research
- If you have been diagnosed with desmoid tumors and have CT (computed tomography) imaging at least twice yearly as part of your standard clinical care, copies of the CT images and the written reports will be collected.

During the biopsy procedures, small pieces of tissue are removed in a similar way to biopsies done for diagnosis. These will be tested and compared to pieces of tissue collected at the end of the study. We are looking for any changes that might have been caused by the study drug.

If all of the exams, tests, and procedures show that you can take part in the study, and you choose to, then you will be provided with:

- Study drug
- A diary to record the study drug you've taken and any symptoms or side effects that you might experience
- Instructions for taking the study drug and completing the diary
- Prescriptions for medications, such as skin cream and antibiotics, to take if needed to help relieve any of the expected symptoms, if they occur.

During the study:

During the study, you will take erlotinib once week, on the same day and approximately the same time each week. You should take the erlotinib at least one hour before or two hours after eating any food. You will be required to keep a diary that notes taking this medication and any other medications you take.

As part of this study you will also be asked to answer questions about your tobacco and alcohol use, both before you begin the study and again at the Month 6 visit. Researchers want to see if tobacco and alcohol use affects the side effects people might get while on this study, or if tobacco and alcohol use modifies the effects of the study agents.

Month 1: You will return for a visit, physical exam, review of your medication diary, review of any symptoms you are experiencing and any medications you are taking. Blood and urine will be collected to check for safety and toxicity.

Approximately Months 2, 4, and 5: You will receive a phone call from the study team to see how you are doing. You will be asked about any symptoms you are experiencing and any medications you are taking.

Month 3: You will return for a visit, physical exam, review of your medication diary, review of any symptoms you are experiencing and any medications you are taking. Your left over study

drug will be collected, and you will be provided with a new supply. Blood and urine will be collected to check for safety and toxicity. Additional optional blood and urine will be collected for research. A pregnancy test will be performed if you are a woman capable of having children.

Month 6 (of if you discontinue participation in the study early for any reason): You will return for a visit, physical exam, review of your medication diary, review of any symptoms you are experiencing and any medications you are taking. You will be asked to complete follow-up assessments of your alcohol and tobacco use, which will take about 10 minutes. Your medication diaries and left over study drug will be collected. Optional blood and urine will be collected for research. Blood and urine will be collected to check for safety and toxicity. A pregnancy test will be performed if you are a woman capable of having children. You will also have another EGD, endoscopy, and biopsy collection to look at your digestive system and evaluate any polyps that are present. You will be asked to complete a short questionnaire about your experience on this study (Was It Worth It?), which should take less than 5 minutes.

If you have been diagnosed with desmoid tumors and have CT (computed tomography) imaging at least twice yearly as part of your standard clinical care, copies of the CT images and the written reports will be collected.

Approximately Month 7: You will be asked about any symptoms you are experiencing and any medications you are taking. If any of the lab tests done at Month 6 were abnormal, they will be repeated at this visit. This visit may be done by telephone if there were no abnormal lab test results.

A study calendar is attached to this document that shows when these tests and procedures will take place.

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

If you choose to take part in the study, there is a risk that you may:

- Lose time at work or home and spend more time in the hospital or doctor's office than usual
- Be asked sensitive or private questions which you normally do not discuss, for example about your tobacco and alcohol use
- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or blood relatives could be found during a study.

The erlotinib 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 urine 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 drugs 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. 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 may have:
• Red and bumpy skin that may itch (Rash) • Loose stool (Diarrhea) • Decreased appetite or not feeling hungry (Anorexia) • Difficulty breathing or shortness of breath (Dsypnea) • Cough • Feeling sick to your stomach (Nausea) • Infection • Throwing up (Vomiting) • Tiredness or fatigue

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving erlotinib, from 4 to 20 may have:
• Sores in the mouth (oral mucositis) • Itching • Acne • Dry skin • Weight loss • Irritation (redness, swelling, warmth, and pain) or infection of the skin around fingernails or toenails • Eye infection/pink eye • Dry eyes • Stomach pain or pain in the abdomen (belly) • Red bumps on the skin that are red, sore, and possibly infected

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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. • Abnormal laboratory result which may indicate liver damage • Liver damage • Kidney damage which may cause swelling, may require dialysis • Swelling, irritation, or scarring of the lungs, which may cause pain or difficulty breathing • A tear or hole in the stomach that may require surgery. More common in people with ulcers (sores in the stomach), diverticulitis (redness, pain, and swelling of part of the belly), and 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 the skin • Patches of skin may become darker in color • Redness, swelling, sores, or a tear or hole in the eye which may cause pain or blurred vision • 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 • Severe diarrhea or vomiting can cause an imbalance of minerals in the blood (called electrolytes) such as low potassium, with symptoms that may include weakness, fatigue, muscle cramps, or constipation • In people with cancer of the pancreas who took combined treatment of erlotinib plus gemcitabine: heart attack, stroke, fever, 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 • Indigestion • Gas in the belly, burping • Irritability (easily annoyed or made angry) • Swelling of the face, hands, feet, or ankles • Runny nose • Dizziness • Headache • Blood clot in the lung which may cause pain, shortness of breath • Stroke (stoppage of blood flow to your brain which may cause paralysis, weakness, headache) • Death or injury to unborn baby • Because of the potential harm to the infant, women should be advised against breast-feeding while receiving erlotinib therapy

Risks of the blood draw: You may have pain, bruising, a blood clot, or rarely, an infection at the site of the needle stick. You may be asked to avoid donating blood during and for one month after you stop taking a study drug.

Risks of the EGD/Lower endoscopy with biopsies: There is a very small risk that the scope may cause a hole in the wall of your throat or stomach. If that were to happen, the doctor will arrange for surgery to repair it. There is a very small risk of bleeding related to the biopsy.

There is a small risk that you will have a reaction to the drugs that are given to make you more comfortable during the EGD procedure. You may have slowed breathing, a slowed heart rate, or you may feel sick to your stomach as the drugs wear off.

You should not drive, sign legal documents, or perform other similar activities for 24 hours after the procedure. You will need to arrange for someone to drive you home after the EGD procedures.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study and for at least 14 days after stopping the study drug. The study drug, 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.

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 must not smoke or use any tobacco products. Urine tests will be done to check your exposure to tobacco and tobacco smoke. Smoking interferes with the way erlotinib works.
- While participating in the study, you must not take more than 81 mg aspirin (1 baby aspirin) per day or more than 650 (two adults-sized tablets) per week.
- While participating in the study, you must not take medications that change the acidity of your digestive tract, such as Protocol Pump Inhibitors (PPIs) for gastric reflux. If you have a prescription for a PPI, and your doctor believes it is safe, an alternative medication can be suggested. However, you will still have to skip this medication on the day before and the day of your erlotinib dose.
- 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?

This study may or may not help you because we do not know how the study drugs will compare to the usual approach for 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.

For the tobacco and alcohol use questions, you can decide to not answer some or all of the questions. Your decision will not affect whether you can participate in the study, and it will not affect your relationship with your doctor or the study staff.

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 Institutional Review Board at *<telephone number>*.

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.

The study will pay for the following:

- Erlotinib
- Medications to help manage common side effects
- Physical exams
- Blood and urine tests
- Blood and urine collection for optional research
- Pregnancy tests, if applicable
- EGD and/or lower GI Endoscopy exams that do not occur at time points that are the same as your usual and routine clinical care
- Questionnaires and medication diaries
- Phone calls to check on side effects and symptoms

You or your insurance company will pay for the following:

- Medications needed to manage uncommon or severe side effects, if they occur

- EGD and/or lower GI Endoscopy exams, if they are completed at a time point that is the same as your usual and routine clinical care

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.

Will I be paid for participating in this study?

You will not be paid for participating in this study. However, at the end of your study participation, you may receive a payment of up to $400 to help cover expenses related to study participation. If you complete only part of the study, you will receive part of this total payment. For example, if you complete half (3 months) of the study, you would receive half of the total payment.

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.

The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance coverage, you would be responsible for any costs. Even though you are in a study, you keep all of your legal rights to receive payment for injury caused by medical errors.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

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 study sponsor, National Cancer Institute, Division of Cancer Prevention
- The Central Institutional Review Board, CIRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the US, and similar organizations if other countries are involved in the study.
- **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 Web site 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 U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the *<name>,* at *<telephone number>* about any questions or concerns you have about this study or to report side effects or injuries.

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.

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Optional Specimen Collections for Laboratory Studies and/or Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer and other health problems. Much of this research is done using specimens from your biopsies, blood, and urine. 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.

If you choose to take part, your blood, your urine, and specimens of your tissue will be collected. The researchers ask your permission to store and use your specimens and health information for medical research. The research that may be done is unknown at this time. Storing specimens for future studies is called “biobanking”. The Biobank is being run by the Cancer Prevention Network (CPN) at the Mayo Clinic and supported by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

- About 20 milliliters of blood will be collected from a vein in your arm.
- A specimen of your urine will be collected.
- Any tissue specimens collected during your endoscopy exams that are left over after the analyses described in the first part of this consent form are complete will be stored for research.
- Your specimens and some related information will be stored in the Biobank at the Mayo Clinic along with specimens from other people who choose to take part.
- The specimens will be kept stored at the Mayo Clinic until the end of the study, when they may be transferred to the National Institutes of Health.
- Qualified researchers can submit a request to use the materials stored in the Biobank. A research committee 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 doctor will be notified if/when research is conducted using your specimens.
- Some of your genetic and health information may be placed in the central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

Samadder NJ, *et al. Gut* 2023; 72:256–263. doi: 10.1136/gutjnl-2021-326532

WHAT ARE THE POSSIBLE RISKS?

- The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
- There are no known risks associated with collection of urine.
- The most common risks related to the biopsy collection are bleeding and nausea, or other symptoms, as the drugs used to make you more comfortable during the procedure wear off. There is a small risk of a hole in your throat or stomach.
- 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.
- A new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:
    - Health insurance companies and group health plans may not request your genetic information that we get from this research.
    - Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment. All health insurance companies and group health plans must follow this law by May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009.

Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. 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:

- When your specimen is sent to the researchers, no information identifying you (such as your name or social security number) will be sent. Specimens will be identified by a unique study code only.

- The list that links the unique code to your name will be kept separate from your specimen and health information. Any Biobank and National Cancer Institute staff with access to the list must sign an agreement to keep your identity confidential.
- Researchers to whom the National Cancer Institute sends your specimen 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.
- Information that identifies you will not be given to anyone, unless required by law.
- If 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 specimens from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. 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.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your specimens to be used, you can call the study doctor, <*name>,* at <*telephone number*> who will let the researchers know. Then, any specimen that remains in the bank will no longer be used. Specimens or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your specimens for research, contact the study doctor, <*name>,* at <*telephone number>.*

Please circle your answer to show whether or not you would like to take part in each option:

SPECIMENS AND RESULTS FOR THE LABORATORY STUDIES:

I agree that my study doctors, or their representative, may contact me or my physician to see if I wish to learn about results from this study.

YES NO

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SPECIMENS AND INFORMATION FOR FUTURE RESEARCH STUDIES:

My blood, urine, and/or tissue specimens and related information may be kept in a Biobank for use in future to learn about, prevent, treat, or cure cancer and other health problems.

YES NO

The information from my tobacco and alcohol use questionnaires may be used in future health research.

YES NO

My blood, urine, and/or tissue specimens and related information may be given to researchers at outside institutions

YES NO

I agree that my study doctors, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

YES NO

This is the end of the section about optional studies.

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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_____

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Study Calendar

Time Point/Visit	Tests and Procedures
Screening	• Sign informed consent document • Physical exam with review of vital signs (pulse, blood pressure, height, weight, temperature) • Review of existing symptoms and medications you are taking • Alcohol and Tobacco Use Assessment • Review of your medical history • Blood and urine tests • Optional blood and urine collection for research • Pregnancy test, if applicable
EGD	• Esophagogastroduodenoscopy (EGD) and a lower gastrointestinal (GI) exam with biopsies
Registration	• Receive instructions for completing diaries and taking medication • Receive 3-month supply of study drug
Day 1	• Starting on Day 1, take study drug with water once a week, at about the same date and time, at least one hour before or two hours after eating any food.
Month 1	• Physical exam with review of vital signs (pulse, blood pressure, height, weight, temperature) • Review of side effects and symptoms you are experiencing and any medications you are taking • Blood and urine tests
Months 2, 4, 5	• Phone call to see how you are doing, ask about side effects, and ask about any medications you are taking
Month 3	• Physical exam with review of vital signs (pulse, blood pressure, height, weight, temperature) • Review of side effects and symptoms you are experiencing and any medications you are taking • Blood and urine tests • Optional blood and urine collection for research • Pregnancy test, if applicable • Collect your diaries and any unused study agent • Receive 3-month supply of study agent and new diaries
Month 6 (or early study termination)	• Physical exam with review of vital signs (pulse, blood pressure, height, weight, temperature) • Review of side effects and symptoms you are experiencing and any medications you are taking • Blood and urine tests • Optional blood and urine collection for research • Pregnancy test, if applicable

	• Collect your diaries and any unused study agent • Follow up assessment of your alcohol and tobacco use • Esophagogastroduodenoscopy (EGD) and possibly a lower gastrointestinal (GI) exam with biopsies • Questionnaire (Was It Worth It), which will take about 5 minutes
Month 7	• Phone call or clinical visit to see how you are doing, ask about side effects, and ask about any medications you are taking. • If any of the blood test results at Month 6 were abnormal, they will be repeated.

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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.

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APPENDIX B
Medication and Symptom Diary

Participant ID _____ Study physician _____

Instructions: This is a checklist for you to use to record taking your study drug.
Please remember that the study drug is to be taken without food. Do not eat for 2 hours before you take the medication or 1 hour after you take the medication. One suggestion would be to take the medication when you first get up in the morning, and then wait at least 1 hour before you have breakfast. On the back of this form, please note any side effects or symptoms you experience and any new medications (prescription, over-the-counter, or supplements).

Week	Date drug was taken	Time drug was taken	Fasting? Yes/No	Time and date of last meal
Example: ☒ *Week 1*	*11/21/2018*	*6:15 a.m.*	*Yes*	*11/20/2018 6:30 p.m.*
☐ **Week 1**		☐ Am ☐ Pm		
☐ **Week 2**		☐ Am ☐ Pm		
☐ **Week 3**		☐ Am ☐ Pm		
☐ **Week 4**		☐ Am ☐ Pm		
☐ **Week 5**		☐ Am ☐ Pm		
☐ **Week 6**		☐ Am ☐ Pm		
☐ **Week 7**		☐ Am ☐ Pm		
☐ **Week 8**		☐ Am ☐ Pm		
☐ **Week 9**		☐ Am ☐ Pm		
☐ **Week 10**		☐ Am ☐ Pm		
☐ **Week 11**		☐ Am ☐ Pm		
☐ **Week 12**		☐ Am ☐ Pm		
☐ **Week 13**		☐ Am ☐ Pm		

☐ **Week 14**		☐ Am ☐ Pm		
☐ **Week 15**		☐ Am ☐ Pm		
☐ **Week 16**		☐ Am ☐ Pm		
☐ **Week 17**		☐ Am ☐ Pm		
☐ **Week 18**		☐ Am ☐ Pm		
☐ **Week 19**		☐ Am ☐ Pm		
☐ **Week 20**		☐ Am ☐ Pm		
☐ **Week 21**		☐ Am ☐ Pm		
☐ **Week 22**		☐ Am ☐ Pm		
☐ **Week 23**		☐ Am ☐ Pm		
☐ **Week 24**		☐ Am ☐ Pm		
☐ **Week 25**		☐ Am ☐ Pm		
☐ **Week 26**		☐ Am ☐ Pm		

Remember: There are a few foods, medications, and activities that may have an impact on the effectiveness of the study drug. Please:

- If you use medications for acid reflux or heartburn symptoms, check with your study doctor to make sure you're using the correct medication. Do not take any reflux or heartburn medication on the day before or the day of taking your study drug, erlotinib.
- Avoid grapefruit-containing products such as grapefruits, grapefruit juice, and any sodas that contain grapefruit juice (Fresca® and Squirt®).
- You must not smoke or use any tobacco products. Urine tests will be done to monitor the amount of tobacco and smoke you are exposed to.
- Be sure to inform the study team of any new medications, including over-the-counter medications, prescription drugs, and dietary supplements.
- Do not take more than 81 mg (1 baby aspirin) daily or 650 mg (2 adult tablets) weekly of aspirin or other NSAIDS.

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Side Effects and Symptoms: Please list any side effects or symptoms you experience, including the dates they started and the dates they stopped. Please list any other medications you took, including starting and stopping dates. If you experience a severe rash or shortness-of-breath, contact your study doctor right away.

Samadder NJ, *et al. Gut* 2023; 72:256–263. doi: 10.1136/gutjnl-2021-326532

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APPENDIX C
Was It Worth It (WIWI) Questionnaire

Visit type (Time point): _____

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

_____ _____
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Appendix D. Alcohol Assessment: Baseline

Instructions: For the following questions about drinking alcoholic beverages, a drink means a 12 oz. beer, a 5 oz. glass of wine, or one and a half ounces of liquor.

1. In your entire life, have you had at least 12 drinks of any kind of alcoholic beverage? *(check one)*
   - ☐ Yes
   - ☐ No **(End)**
   - ☐ Choose not to answer **(End)**
   - ☐ Don't know/Not sure

   (If No or Choose not to answer), stop assessment

2. In the past 12 months, on average, how often did you drink any type of alcoholic beverage? *(Enter the number of days you drank based on the timeframe checked below. Enter 0 if you never drank and skip to Question 6.)* _____
   (If more than 0, check one)
   - ☐ Week
   - ☐ Month
   - ☐ Year
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

3. In the past 12 months, on those days that you drank alcoholic beverages, on average, how many drinks did you have per day?
   *(Enter the average number of drinks per day)*_____
   (If no answer, check one)
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

4. In the past 12 months, on how many days did you have 5 or more drinks of any alcoholic beverage?
   *(Enter the number of days you had 5 or more drinks, or enter 0 if none.)*_____
   (If no answer, check one)
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

5. Was there ever a time or times in your life when you drank 5 or more drinks of any kind of alcoholic beverage almost every day?
   (check one)
   - ☐ Yes
   - ☐ No
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

6. If you do not currently drink alcoholic beverages, but did in the past, how long has it been since you last drank regularly?
   (check one)
   - ☐ Within the past month (0 to 1 month ago)
   - ☐ Between 1 and 3 months (1 to 3 months ago)
   - ☐ Between 3 and 6 months (3 to 6 months ago)
   - ☐ Between 6 and 12 months (6 to 12 months ago)
   - ☐ Between 1 and 5 years (1 to 5 years ago)
   - ☐ Between 5 and 15 years (5 to 15 years ago)
   - ☐ More than 15 years ago
   - ☐ Don't know/Not sure
   - ☐ Never drank regularly
   - ☐ Choose not to answer

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Alcohol Assessment: Baseline (continued)

7. At the heaviest point, either now or in the past, on the days when you drank, about how many drinks did you drink a day on the average? *(Enter the number of drinks a day)*_____
(If no answer, check one)
☐ Choose not to answer
☐ Don't know/Not sure

8. How many years have you been drinking (or did drink) regularly? _____ years
(If no answer, check one)
☐ Choose not to answer
☐ Don't know/Not sure

9. At what age did you begin drinking regularly? _____ years of age
(If no answer, check one)
☐ Choose not to answer
☐ Don't know/Not sure

10. What type(s) of alcohol do you drink?

Wine	*(check one)* ☐ Yes	☐ No	☐ Choose not to answer
Liquor	*(check one)* ☐ Yes	☐ No	☐ Choose not to answer
Beer	*(check one)* ☐ Yes	☐ No	☐ Choose not to answer
Wine cooler	*(check one)* ☐ Yes	☐ No	☐ Choose not to answer

_____ _____
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Appendix D. Alcohol Assessment: Follow-Up

Instructions: For the following questions about drinking alcoholic beverages, a drink means a 12 oz. beer, a 5 oz. glass of wine, or one and a half ounces of liquor.

1. During the past 30 days, did you drink any alcoholic beverages? *(check one)*
   - ☐ Yes
   - ☐ No **(End)**
   - ☐ Choose not to answer **(End)**
   - ☐ Don't know/Not sure

   (If No or Choose not to answer, stop assessment)

2. During the past 30 days, how many days per week or per month did you drink any alcoholic beverages, on the average?
   (Enter number of days you drank based on the timeframe checked below. Enter 0 if you did not drink.) _____
   (If more than 0), specify *(check one)*
   - ☐ Week
   - ☐ Month
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

3. On the days when you drank, on average, about how many drinks did you have?
   (Enter the average number of drinks you had per day.) _____
   (If no answer, check one)
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

4. In the past 30 days, on how many days did you have 5 or more drinks per day? _____
   (Enter the number of days you had 5 or more drinks, or enter 0 if none)
   (If no answer, check one)
   - ☐ None
   - ☐ Choose not to answer
   - ☐ Do not know/Not sure

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Appendix D. Tobacco Assessment: Baseline

Section A. Basic Cigarette Use Information

1. Have you smoked at least 100 cigarettes (5 packs = 100 cigarettes) in your entire life?
   - ☐ Yes
   - ☐ Choose not to answer → **Skip to Section B**
   - ☐ No → **Skip to Section B**
   - ☐ Don't know/Not sure → **Skip to Section B**

2. How old were you when you first smoked a cigarette *(even one or two puffs)*? _____ Years old
   (If no answer, check one)
   ☐ Choose not to answer ☐ Don't know/Not sure

3. How old were you when you first began smoking cigarettes regularly? _____ Years old
   (If no answer, check one)
   ☐ Refused ☐ Don't know/Not sure ☐ Check here if you have never smoked cigarettes regularly.

4. How many total years have you smoked (or did you smoke) cigarettes? Do not count any time you may have stayed off cigarettes.
   (If you smoked less than one year, write "1.") _____ Years
   ☐ Choose not to answer ☐ Don't know/Not sure

5. On average when you have smoked, about how many cigarettes do you (or did you) smoke a day? *(A pack usually has 20 cigarettes in it).* _____ Number of cigarettes per day
   (If no answer, check one)
   ☐ Choose not to answer ☐ Don't know/Not sure

6. Do you NOW smoke cigarettes? *(check one)*
   - ☐ Everyday
   - ☐ Some days
   - ☐ Choose not to answer → **Skip to question 8**
   - ☐ Not at all → **Skip to question 8**

7. How soon after you wake up do you smoke your first cigarette? *(check one)*
   ☐ Within 30 minutes ☐ After 30 minutes ☐ Choose not to answer

8. How long has it been since you last smoked a cigarette (even one or two puffs)? *First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.*

   I smoked a cigarette today (at least one puff) *(check one)* ☐ Yes ☐ No
   1-7 days *(check one)* ☐ Yes ☐ No
   (If yes), Number of days since last cigarette _____
   Less than 1 month *(check one)* ☐ Yes ☐ No
   (If yes), Number of weeks since last cigarette _____
   Less than 1 year *(check one)* ☐ Yes ☐ No
   (If yes), Number of months since last cigarette _____
   More than 1 year *(check one)* ☐ Yes ☐ No
   (If yes), Number of years since last cigarette _____
   Don't know/Don't remember *(check one)* ☐ Yes ☐ No
   Choose not to answer ☐

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Tobacco Assessment: Baseline (continued)

Section B. Use of Other Forms of Tobacco

9. Have you ever used other forms of tobacco, not including cigarettes? *(check one)*
☐ Yes ☐ Choose not to answer
☐ No → **Skip to Section C**

10. How often do you/did you use other forms of tobacco?
Every day *(check one)* ☐Yes ☐No *(If yes)*, Number of times per day _____
Some days *(check one)* ☐Yes ☐No *(If yes)*, Number of days _____
(If yes), Per *(select one)* ☐ Week ☐ Month ☐Year

11. Which of the following products have you ever used regularly? *(Mark yes, no., or choose not to answer for all choices)*

Cigarettes	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Traditional cigars, cigarillos or filtered cigars	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Hookah	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Bidis	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Snus	*(check one)* ☐Yes ☐No ☐ Choose not to answer
E-cigarettes or other electronic nicotine delivery system	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Pipes	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Waterpipe	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Clove cigarettes or kreteks	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Smokeless tobacco *(like dip, chew, or snuff)*	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Paan with tobacco, gutka, zarda, khaini	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Other, please specify: _____	

12. If you do not currently use other forms of tobacco, but did in the past, how long has it been since you last used other forms of tobacco regularly? *(check one)*
☐ Within the past month (0 to 1 month ago)
☐ Between 1 and 3 months (1 to 3 months ago)
☐ Between 3 and 6 months (3 to 6 months ago)
☐ Between 6 and 12 months (6 to 12 months ago)
☐ Never used other forms of tobacco regularly
☐ Between 1 and 5 years (1 to 5 years ago)
☐ Between 5 and 15 years (5 to 15 years ago)
☐ More than 15 years ago
☐ Don't know/Not sure
☐ Choose not to answer

Section C. Second-Hand Smoke Exposure

13. Are you currently living with a smoker? *(check one)*
☐Yes ☐No ☐ Choose not to answer

14. In the past 30 days, have you lived in a place where other people smoked cigarettes indoors? *(check one)*
☐Yes ☐No ☐ Choose not to answer

15. In the past 30 days, have you worked in a place where other people smoked cigarettes indoors? *(check one)*
☐Yes ☐No ☐ Choose not to answer

16. Thinking of all your childhood and adult years, have you ever lived in a place where other people smoked cigarettes indoors? *(check one)*
☐Yes → In total, for about how many years? _____ If less than 1, write "1."
☐No
☐ Choose not to answer

17. Thinking of all the years you have worked, have you ever worked in a place where other people smoked cigarettes indoors? *(check one)*
☐Yes → In total, for about how many years? _____ If less than 1, write "1."
☐No
☐ Choose not to answer

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Appendix D. Tobacco Assessment: Follow-Up

1. Do you NOW smoke cigarettes? *(check one)*
   - ☐ Everyday
   - ☐ Some days
   - ☐ Choose not to answer→ **Skip to Question 4.**
   - ☐ Not at all → **Skip to Question 4.**

2. On average, when you smoked, about how many cigarettes do you (or did you) smoke a day? *(A pack usually has 20 cigarettes in it)*.
   _____ Number of cigarettes per day
   (If no answer, check one)
   ☐Choose not to answer ☐Don't know/Not sure

3. How long has it been since you last smoked a cigarette (even one or two puffs)? *First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.*
   I smoked a cigarette today (at least one puff) *(check one)* ☐Yes ☐No
   1-7 days *(check one)* ☐Yes ☐No
   (If yes), Number of days since last cigarette _____
   Less than 1 month *(check one)* ☐Yes ☐No
   (If yes), Number of weeks since last cigarette _____
   Less than 1 year *(check one)* ☐Yes ☐No
   (If yes), Number of months since last cigarette _____
   More than 1 year *(check one)* ☐Yes ☐No
   (If yes), Number of years since last cigarette _____
   Don't know/Don't remember *(check one)* ☐Yes ☐No
   Choose not to answer ☐

4. Since your last visit, have you used other forms of tobacco, not including cigarettes? *(check one)*
   - ☐ Yes
   - ☐ Choose not to answer **(End)**
   - ☐ No (**End)** *(If no)*, stop assessment

5. How often do you/did you use other forms of tobacco?
   Every day *(check one)* ☐Yes ☐No *(If yes),* Number of times per day _____
   Some days *(check one)* ☐Yes ☐No *(If yes),* Number of days _____
   (If yes), per *(select one)* ☐Week ☐Month ☐Year
   ☐Choose not to answer

6. Since your last visit, which of the following products have you used? *(Mark yes or no for all choices)*

Cigarettes	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Traditional cigars, cigarillos or filtered cigars	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Hookah	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Bidis	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Snus	*(check one)* ☐Yes ☐No ☐ Choose not to answer
E-cigarettes or other electronic nicotine delivery system	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Pipes	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Waterpipe	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Clove cigarettes or kreteks	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Smokeless tobacco *(like dip, chew, or snuff)*	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Paan with tobacco, gutka, zarda, khaini	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Other, please specify: _____	

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Tobacco Assessment: Follow-Up (continued)

7. If you do not currently use other forms of tobacco, but did in the past, how long has it been since you last used other forms of tobacco regularly? *(check one)*
   - ☐ Within the past month (0 to 1 month ago)
   - ☐ Between 1 and 3 months (1 to 3 months ago)
   - ☐ Between 3 and 6 months (3 to 6 months ago)
   - ☐ Between 6 and 12 months (6 to 12 months ago)
   - ☐ Between 1 and 5 years (1 to 5 years ago)
   - ☐ Between 5 and 15 years (5 to 15 years ago)
   - ☐ More than 15 years ago
   - ☐ Don't know/Not sure
   - ☐ Choose not to answer
   - ☐ Never used other forms of tobacco regularly

The following instructions pertain to questions 8 -10. During each of the following time frames, please indicate whether you smoked cigarettes every day, some days, or not at all.

8. During study treatment *(check one)*
   - ☐ Smoked every day
   - ☐ Smoked some days
   - ☐ Did not smoke at all
   - ☐ Don't know/not sure
   - ☐ Choose not to answer
   - ☐ Not applicable

9. After the end of study treatment *(check one)*
   - ☐ Smoked every day
   - ☐ Smoked some days
   - ☐ Did not smoke at all
   - ☐ Don't know/not sure
   - ☐ Choose not to answer
   - ☐ Not applicable (I have not completed the study treatment)

10. Since your last visit to this clinic *(check one)*
   - ☐ Smoked every day
   - ☐ Smoked some days
   - ☐ Did not smoke at all
   - ☐ Don't know/not sure
   - ☐ Choose not to answer
   - ☐ Not applicable (This is my first visit to this clinic)

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Appendix E. Alcohol and Tobacco Cessation Resources

National and local resources to help with alcohol abuse and alcoholism

NIAAA's online guide ***Treatment for Alcohol Problems: Finding and Getting Help*** is written for individuals, and their family and friends, who are looking for options to address alcohol problems. It is intended as a resource to understand what treatment choices are available and what to consider when selecting among them.
https://pubs.niaaa.nih.gov/publications/treatment/treatment.htm

Other resources:

National Institute on Alcohol Abuse and Alcoholism www.niaaa.nih.gov
301–443–3860

National Institute on Drug Abuse www.nida.nih.gov
301–443–1124

National Clearinghouse for Alcohol and Drug Information www.samhsa.gov
1–800–729–6686

Substance Abuse Treatment Facility Locator www.findtreatment.samhsa.gov
1–800–662–HELP

Alcoholics Anonymous (AA) www.aa.org
212–870–3400 or check your local phone directory under "Alcoholism"

Moderation Management www.moderation.org
212–871–0974

Secular Organizations for Sobriety www.sossobriety.org
323–666–4295

SMART Recovery www.smartrecovery.org
440–951–5357

Women for Sobriety www.womenforsobriety.org
215–536–8026

Al-Anon Family Groups www.al-anon.alateen.org
1–888–425–2666 for meetings

Adult Children of Alcoholics www.adultchildren.org
310–534–1815

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National and local resources to help with quitting smoking

NCI's Smokefree.gov offers science-driven tools, information, and support that has helped smokers quit. You will find state and national resources, free materials, and quitting advice from NCI.

Smokefree.gov was established by the Tobacco Control Research Branch of NCI, a component of the National Institutes of Health, in collaboration with the Centers for Disease Control and Prevention and other organizations.

Publications available from the Smokefree.gov Web site include the following:

- Clearing the Air: Quit Smoking Today for smokers interested in quitting.
- Clear Horizons for smokers over age 50.
- Forever Free™ for smokers who have recently quit.
- Forever Free for Baby and Me™, in English and Spanish, for pregnant smokers who have recently quit.
- Pathways to Freedom: Winning the Fight Against Tobacco for African American smokers.

NCI's Smoking Quitline at **1–877–44U–QUIT (1–877–448–7848)** offers a wide range of services, including individualized counseling, printed information, referrals to other resources, and recorded messages. Smoking cessation counselors are available to answer smoking-related questions in English or Spanish, Monday through Friday, 8:00 a.m. to 8:00 p.m., Eastern Time. Smoking cessation counselors are also available through LiveHelp, an online instant messaging service. LiveHelp is available Monday through Friday, 8:00 a.m. to 11:00 p.m., Eastern Time.

Your state has a toll-free telephone quitline. Call **1–800–QUIT–NOW (1–800–784–8669)** to get one-on-one help with quitting, support and coping strategies, and referrals to resources and local cessation programs. The toll-free number routes callers to state-run quitlines, which provide free cessation assistance and resource information to all tobacco users in the United States. This initiative was created by the Department of Health and Human Services. For more information about quitlines, speak to an expert on the Smokefree.gov Web site.

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Appendix F. Diary of Medications Used for Acid Reflux Symptoms

Participant ID _____ Study physician _____

Instructions: Use this diary to record any medications used for symptoms related to acid reflux or upset stomach. Use the back of this page for any other notes or comments.

REMEMBER: These medications may interfere with the effectiveness of erlotinib. You are asked to avoid these medications on the day before and the day you actually take your weekly erlotinib. Please let your study team know if you have any questions or problems.

Date/Time	Name of antacid taken	Dose	Name of H2 receptor agonist	Dose
Example: 1/11/2018 8:00 p.m.	*Tums – Extra strength*	*2 tablets = 1500 mg*		
Example: 1/19/2018 8:00 p.m.			*ranitidine*	*150 mg*

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Date/Time	Name of antacid taken	Dose	Name of H2 receptor agonist	Dose

_____ _____
Participant signature Date