Introduction

This study is a randomized, placebo-controlled, phase II trial designed to determine if the combination of sulindac and erlotinib causes a significant regression of duodenal adenomas in familial adenomatous polyposis (FAP) and attenuated FAP patients. The study is an intention to treat design.

Data

This is a completely randomized clinical trial. Subjects were randomized to drug or placebo. The total sample size originally proposed for the trial was 100 patients, randomized 1:1 between treatment and placebo. There were two planned interim analyses. After the 2nd interim analysis it was determined that the trial should be stopped after those scheduled to complete their end points by June 30th were finished. Data is maintained in a database for the purposes of linking study data with other medical visit information. Data used in the analyses was provided in excel files. Due to blinding, the pharmacy group provided treatment allocation for randomized subjects. At final enrollment there were 78 randomized and 73 who had data for baseline and endpoint endoscopy (5 withdrew). Data was collected during a baseline esophagogastroduodenoscopy (EGD) and colonoscopy as well as a final EGD and colonoscopy. Duodenal segments had size of polyps and count of polyps recorded. When a large number of duodenal polyps are detected (>75) the count recorded reflects an estimate of count to the nearest 25 or 50. Nonparametric methods will be used primarily in this analysis to protect against outliers. Total sum of diameters of duodenal polyps within a given area is also a primary outcome of interest. This document also refers to total colorectal polyp counts or sum of diameters within the colorectal area available for examination. It will be necessary to stratify by the amount of remaining colon, since patients that had previous colectomy procedures have had portions of the colon and rectum removed and polyps will only be found in the remaining segments. Use of proton pump inhibitors could be at time of enrollment or the subject may be prescribed proton pump inhibitors within the study. For the purpose of this analysis we will define anyone who was put on PPI by 3 months (90 days) into the study period as PPI use. Otherwise subjects will be categorized as no PPI use.
Research Objectives

Primary Objective
The combination of sulindac and erlotinib is hypothesized to cause a significant regression of duodenal adenomas in familial adenomatous polyposis (FAP) and attenuated FAP patients. Significant regression will be determined to exist if the change in the total polyp burden in the treatment arm is significantly different from the change in total duodenal polyp burden in the placebo arm. The duodenal polyp burden will be calculated as the sum of the diameters of polyps in a marked 10-cm duodenal segment. Change is measured as the difference between the duodenal polyp burden following six months of treatment and the duodenal polyp burden at baseline.

Key Secondary Objectives

Duodenal Polyps Secondary Objectives
For secondary objectives listed below, “duodenal polyp burden” will be calculated as defined in the Primary Objective.

1. Compare the change in duodenal polyp number between treatment arms
2. Compare the change in total duodenal polyp burden between treatment arms, stratified by total initial duodenal polyp burden low vs. high, defined by the median split. Duodenal polyp burden is defined as in the Primary Objective.
3. Compare the change in duodenal polyp burden between treatment arms, stratified by largest single polyp at baseline, with initial duodenal polyp group small vs. large, defined by the median split.
4. Relate the change in duodenal polyp burden in the active treatment arm to the presence of CTCAE v4.0 Grade 1 or greater acne rash.
5. Compare the change in duodenal polyp burden between treatment arms, stratified by AFAP or FAP diagnosis.
6. Relate the change in duodenal polyp burden in the active treatment arm to the administered total dose of erlotinib, which is calculated from the number of pills dispensed minus the number of pills returned minus the number of pills reported as lost.
7. Relate the change in duodenal polyp burden in the active treatment arm to the administered total dose of sulindac, which is calculated from the number of pills dispensed minus the number of pills returned minus the number of pills reported as lost.
8. Relate the change in total duodenal polyp burden in the active treatment arm to the use of proton pump inhibitors (PPI) defined as taking PPI any time before 3-month time point on trial.
**Colorectal Polyp Secondary Objectives**

For the colorectal polyp objectives listed below, separate analysis will be performed in the following strata of patients:

- **a)** Patients with complete colon or at least 30 cm of remaining colon
- **b)** IPPA (ileal J-pouch or ileoanal anastomosis)
- **c)** Ileorectal (<30 cm of remaining colon).

Patients with an ileostomy will be excluded from analyses of colorectal polyps.

- **9.** Compare the change in total colorectal polyp number between treatment arms, stratified as above.
- **10.** Relate the change in colorectal polyp burden in the active treatment arm to the presence of acne rash, stratified and defined as above.
- **11.** Relate the change in colorectal polyp burden in the active treatment arm to the administered total dose of erlotinib, stratified and defined as above.
- **12.** Relate the change in colorectal polyp burden in the active treatment arm to the administered total dose of sulindac, stratified and defined as above.
- **13.** Relate the change in total colorectal polyp burden in the active treatment arm to the use of proton pump inhibitors (PPI), stratified and defined as above.

**Exploratory Objectives**

- **14.** Measure changes in COX-2 expression, IL-17 expression, EGFR phosphorylation, MEK1 phosphorylation, AKT phosphorylation, Ki-67 expression and/or cyclin D1 expression in intestinal polyps and normal intestinal mucosa with treatment.
- **15.** Determine β-catenin localization in adenomatous intestinal polyps with or without oncogenic KRAS mutations.
- **16.** Determine differentially expressed mRNA by performing RNA sequencing 20 endpoint patient paired normal and tumor (10 on placebo and 10 on drug). The 20 will be selected based on 1) availability of polyp with preference toward larger polyp biopsy 2) patients who demonstrated the extreme of response (placebo who had the largest % increase in sum diameter and drug who had the largest % decrease in sum diameter.
Analyses

Study demographics within treatment will be described in a table. Variables currently available are Sex, Age at baseline, FAP/AFAP, Height, Weight (or BMI) at baseline, Alcohol use at baseline (yes/no) and smoker at baseline (yes/no). Additionally, subjects on PPI at 0-3 months will be described here.

Study events will be described by treatment arm. Events included will be study withdrawal, short list of adverse events, PPI prescribed during study.

Primary Objective

The two-sided Wilcoxon-Mann-Whitney test will be used to test a significant difference between treatment arms in the change in duodenal polyp burden. The duodenal polyp burden will be calculated as the sum of the diameters of polyps in a marked 10-cm duodenal segment. Change is measured as the difference between the duodenal polyp burden following six months of treatment and baseline.

Analysis of Key Secondary Objectives

For secondary objectives “duodenal polyp burden” will be calculated as defined in the Primary Objective.

1. The change in duodenal polyp number between treatment arms will be tested for significance with two-sided Wilcoxon-Mann-Whitney test.

2. The change in duodenal polyp burden between treatment arms will be tested for significance with two-sided Wilcoxon-Mann-Whitney test within each stratum: Low or High total initial duodenal polyp burden.

3. The change in duodenal polyp burden between treatment arms will be tested for significance with two-sided Wilcoxon-Mann-Whitney test within each of the following strata: below and above median largest initial duodenal polyp group.

4. The change in duodenal polyp burden between treatment arms will be tested for significance with two-sided Wilcoxon-Mann-Whitney test within each of the following strata: AFAP or FAP phenotype.

5. The association of the change in duodenal polyp burden and acne rash in the active treatment arm with the presence of acne rash will be tested for significance with two-sided Wilcoxon-Mann-Whitney test.

6. Robust linear regression will be used to test the association of the change in duodenal polyp burden in the active treatment arm to the administered total dose of erlotnib.
7. Robust linear regression will be used to test the association of the change in duodenal polyp burden in the active treatment arm to the administered total dose of sulindac.

8. The relationship of the change in total duodenal polyp burden in the active treatment arm to the use of proton pump inhibitors (PPI) will be tested for significance with two-sided Wilcoxon-Mann-Whitney test. PPI will be categorized as a Yes/No variable. Patients on PPI up to month 3 on study will be classified as “Yes”. Patients never on PPI or placed on PPI after month 3 on study will be classified as “No”.

Analysis of Colorectal Polyp Objectives

Separate analysis of colorectal polyps will be performed in the following strata of patients:

- d) Patients with complete colon or at least 30 cm of remaining colon
- e) IPPA (ileal J-pouch or ileoanal anastomosis)
- f) Ileorectal (<30 cm of remaining colon).

Patients with an ileostomy will be excluded from analyses of colorectal polyps.

9. The change in total colorectal polyp number between treatment arms will be tested for significance with two-sided Wilcoxon-Mann-Whitney test within each stratum defined above.

10. The association of the change in colorectal polyp burden and acne rash in the active treatment arm with the presence of acne rash will be tested for significance with two-sided Wilcoxon-Mann-Whitney test in each stratum defined above.

11. Robust linear regression will be used to test the association of the change in colorectal polyp burden in the active treatment arm to the administered total dose of erlotinib in each stratum defined above.

12. Robust linear regression will be used to test the association of the change in colorectal polyp burden in the active treatment arm to the administered total dose of sulindac in each stratum defined above.

13. The relationship of the change in total colorectal polyp burden in the active treatment arm to the use of proton pump inhibitors (PPI) will be tested for significance with two-sided Wilcoxon-Mann-Whitney test in each stratum defined above. PPI will be categorized as a Yes/No variable. Patients on PPI up to month 3 on study will be classified as “Yes”. Patients never on PPI or placed on PPI after month 3 on study will be classified as “No”.

151
**Exploratory Objectives**

Currently the assay methods for the measures listed below have not been determined. Prior to receiving data for these exploratory objectives the statistical analysis plan will be modified to include complete details of analysis of these endpoints, including any categorization of these measures and exploratory hypothesis tests.

14. Measure changes in COX-2 expression, IL-17 expression, EGFR phosphorylation, MEK1 phosphorylation, AKT phosphorylation, Ki-67 expression and/or cyclin D1 expression in intestinal polyps and normal intestinal mucosa with treatment.

15. Determine β-catenin localization in adenomatous intestinal polyps with or without oncogenic KRAS mutations.

16. Determine differentially expressed mRNA by performing RNA sequencing 20 endpoint patient paired normal and tumor (10 on placebo and 10 on drug). The 20 will be selected based on 1) availability of polyp with preference toward larger polyp biopsy 2) patients who demonstrated the extreme of response (placebo who had the largest % increase in sum diameter and drug who had the largest % decrease in sum diameter.

Results will include the effect estimates, confidence intervals and p-values associated with effect of treatment. Results will be reported separately within each treatment arm.

**SDBC Information**

Please remember to acknowledge the SDBC: “This investigation was supported by the University of Utah Study Design and Biostatistics Center, with funding in part from the Huntsman Cancer Institute, the National Cancer Institute through Cancer Center Support P30 CA042014, the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant 8UL1TR000105 (formerly UL1RR025764).”.

[Logo of SDBC]

The University of Utah
Study Design and Biostatistics Center
Center for Clinical and Translational Science
http://www.ccts.utah.edu/biostats/
Genetic Events Leading to APC-Dependent Colon Cancer in High-Risk Families; a clinical trial of COX and EGFR inhibition in familial polyposis patients

Principal Investigator
N. Jewel Samadder, M.D., M.S.C
Assistant Professor of Medicine (GI)
Division of Gastroenterology and Hepatology
Investigator Huntsman Cancer Institute
801-585-9427
Jewel.samadder@hsc.utah.edu

Co-investigator(s)
Randall W. Burt MD
Professor Emeritus
Huntsman Cancer Institute
801-585-3281
Randall.burt@hci.utah.edu

Deborah Neklason, PhD
Research Assistant Professor, Oncological Sciences
University of Utah
801-587-9882
Deb.neklason@hci.utah.edu

John Fang, MD,
Professor of Internal Medicine (Gastroenterology)
University of Utah
School of Medicine
30 N Medical Dr
Salt Lake City, UT 84132
801-581-7802 office
John.fang@hsc.utah.edu

Kathryn Byrne, MD
Clinical Instructor, Gastroenterology
University of Utah
801-581-7803 office
801-339-9342 pager
kathryn.byrne@hsc.utah.edu
Protocol name: Genetic Events Leading to APC-Dependent Colon Cancer in High-Risk Families; a clinical trial of COX and EGFR inhibition in familial polyposis patients.

Version Date: December 15, 2014

Principal Investigator: N. Jewel Samadder, MD

Scott K. Kuwada, MD
Professor of Medicine, Chief, Division Gastroenterology,
University of Hawaii
1356 Lusitana St
Honolulu, HI 96813
808-586-7478
skkuwada@hawaii.edu

Wade Samowitz, MD
Professor of Pathology
University of Utah
(801) 583-2787 x3405
wade.samowitz@aruplab.com

David Jones, PhD
Associate Professor, Oncological Sciences
Huntsman Cancer Institute
(801) 585-6107
David.jones@hci.utah.edu

Matthew K. Topham, MD
Associate Professor, Dept. Internal Medicine
Huntsman Cancer Institute
(801) 585-0304
Matt.topham@hci.utah.edu

Diana M. Stafforini, PhD
Res. Associate Professor, Dept. Internal Medicine
Huntsman Cancer Institute
(801) 585-3402
Diana.stafforini@hci.utah.edu

Melinda Angus-Hill, PhD
Assistant Professor, Dept. Internal Medicine
Huntsman Cancer Institute
(801)213-4240
Melinda.angus-hill@hci.utah.edu

Kathleen Boynton, MD
Assistant Professor Dept Internal Medicine
Gastroenterology
University of Utah
(801)585-2357
Kathleen.boynton@hsc.utah.edu
Protocol name: Genetic Events Leading to APC-Dependent Colon Cancer in High-Risk Families; a clinical trial of COX and EGFR inhibition in familial polyposis patients.
Version Date: December 15, 2014
Principal Investigator: N. Jewel Samadder, MD

Biostatistician
Kenneth M. Boucher PhD
Res Associate Professor, Oncological sciences.
4243 Huntsman Cancer Institute
(801) 585-9544
Ken.boucher@hci.utah.edu

Sponsor
Investigator Initiated
NCI grant PO1–CA073992

Investigational agent
erlotinib (Tarceva)
sulindac
TABLE OF CONTENTS

STUDY SUMMARY ................................................................. 5

1 OBJECTIVES ........................................................................... 8
1.1 Primary Objectives ............................................................ 8
1.2 Secondary Objectives ......................................................... 8

2 BACKGROUND ....................................................................... 8
2.1 Epidermal Growth Factor Receptor Expression and Significance in Cancer ...... 9
2.2 Sulindac as a COX-2 inhibitor ............................................ 10
2.3 The Familial Adenomatous Polyposis Syndromes ..................... 10
2.4 Study Rationale .............................................................. 11

3 DRUG INFORMATION ........................................................... 12
3.1 Description of Erlotinib (Tarceva) ........................................... 12
3.2 Nonclinical Data of Tarceva ................................................. 12
3.3 Clinical Experience with Tarceva .......................................... 13
3.4 Description of Sulindac ..................................................... 15
3.5 Clinical Experience with Sulindac ........................................ 16
3.6 Over-encapsulated Tablets (Blinding of drugs) ......................... 18
3.7 Risks and Known Adverse Reactions ................................. 18

4 STAGING CRITERIA ............................................................. 19

5 ELIGIBILITY CRITERIA ......................................................... 19
5.1 Inclusion Criteria ............................................................. 19
5.2 Exclusion Criteria ............................................................ 20

6 STRATIFICATION FACTORS ............................................... 20

7 TREATMENT PLAN .......................................................... 20
7.1 Administration Schedule .................................................... 21

8 TOXICITIES AND DOSEAGE MODIFICATION ..................... 21
8.1 General Plan to Manage Safety Concerns ............................ 21
8.2 Dose Modifications .......................................................... 23
8.3 Supportive Care .............................................................. 26
8.4 Duration of Therapy ........................................................ 26

9 STUDY CALENDAR ............................................................ 25
9.1 Screening and Pretreatment Assessments ............................. 27
9.2 Evaluations and Procedures During Treatment ..................... 29
9.3 Follow-Up Assessments .................................................... 30

10 SAFETY AND MONITORING ........................................... 30
10.1 Iterim Analyses of Efficacy ................................................ 30
10.2 Safety .............................................................................. 29
10.3 Adherence ........................................................................ 30
10.4 Measurement of Effect .................................................... 30

11 POWER ESTIMATES FOR PRIMARY OBJECTIVE Error! Bookmark not defined.
Protocol name: Genetic Events Leading to APC-Dependent Colon Cancer in High-Risk Families; a clinical trial of COX and EGFR inhibition in familial polyposis patients.

Version Date: December 15, 2014

Principal Investigator: N. Jewel Samadder, MD

12 DISCIPLINE REVIEW
13 REGISTRATION GUIDELINES
14 DATA SUBMISSION SCHEDULE
15 SPECIAL INSTRUCTIONS
15.1 Correlative Studies
15.2 Informed consent
15.3 Institutional Review
15.4 Data Monitoring and Safety Plan
15.5 Adverse Events
15.6 Protocol amendments, or changes in study conduct
15.7 FDA Annual Reporting
15.8 Clinical Trials Data Bank
16 BIBLIOGRAPHY
17 MASTER FORM SET
18 APPENDIX
18.1 APPENDIX A: Study Flowchart
18.2 Appendix B: List of CYP3A4 Inhibitors
18.3 APPENDIX C: Description of Clinical Core C and Analytic Core B of the Program Project Grant
18.4 APPENDIX D: WHO Performance Status Scale
### STUDY SUMMARY

<table>
<thead>
<tr>
<th>Title</th>
<th>Genetic Events Leading to APC-Dependent Colon Cancer in High-Risk Families; a clinical trial of COX and EGFR inhibition in familial polyposis patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Title</td>
<td>Sulindac + Erlotinib in FAP</td>
</tr>
<tr>
<td>Protocol Number</td>
<td>IRB # 39278</td>
</tr>
<tr>
<td>Phase</td>
<td>Phase II</td>
</tr>
<tr>
<td>Methodology</td>
<td>Double blind, randomized placebo controlled.</td>
</tr>
<tr>
<td>Study Duration</td>
<td>5 years</td>
</tr>
<tr>
<td>Study Center(s)</td>
<td>Single-center, University of Utah</td>
</tr>
</tbody>
</table>
| Objectives | **Primary**: To determine if the combination of sulindac and erlotinib causes a significant regression of duodenal adenomas in FAP and attenuated FAP patients.  
**Secondary**:  
1. Measure if combination of sulindac and erlotinib cause a reduction in duodenal polyposis based on Spigelman classification.  
2. Determine if the combination of sulindac and erlotinib causes a significant regression of colorectal adenomas.  
3. Measure changes in COX-2 expression, EGFR phosphorylation, MEK1 phosphorylation, AKT phosphorylation, Ki-67 expression and/or cyclin D1 expression in intestinal polyps and normal intestinal mucosa with treatment.  
4. Determine β-catenin localization in adenomatous intestinal polyps with or without oncogenic KRAS mutations. |
| Number of Subjects | 100 subjects (50 per arm) |
| Diagnosis and Main Inclusion Criteria | Genetic diagnosis of FAP or AFAP and presence of duodenal polyps with a sum diameter of ≥ 5mm. |
| Study Product, Dose, Route, Regimen | Sulindac (150 mg twice daily) + erlotinib (75 mg once daily) or placebo |
| Duration of administration | 6 months |
| Reference therapy | Reference is placebo arm of study |
| Statistical Methodology | The primary endpoint will be 1) a comparison of the total adenomatous polyp burden in the duodenum, measured as the change ΔD in the sum of the diameters of the adenomatous polyps from the duodenal segment. At the end of the 6-month treatment period, all visible polyps will be counted, measured, and recorded as performed in the pretreatment endoscopies. The primary analysis will be via Wilcoxon (Mann-Whitney) tests comparing the sulindac + erlotinib and placebo arms. |
1 OBJECTIVES

1.1 Primary Objectives

To determine in a randomized, placebo-controlled, phase II trial if the combination of sulindac and erlotinib causes a significant regression of duodenal adenomas in familial adenomatous polyposis (FAP) and attenuated FAP patients. The study is a per protocol analysis design.

This will be accomplished by measurement of the following endpoints:

• Change in total duodenal polyp burden, calculated as the sum of the diameters of polyps in a 10-cm duodenal segment, following six months of treatment.

1.2 Secondary Objectives

1. Change in duodenal polyposis based on Spigelman classification (stages 0-IV) based on polyp number, size, histology and severity of dysplasia (Spigelman et al, 1989).

2. Change in total colorectal (for those with an intact colon or rectal stump and choosing to undergo colonoscopy) adenomatous polyp burden, calculated as the sum of the diameters of adenomatous polyps in the colon and/or rectum following six months of treatment.

3. Measure changes in COX-2 expression, EGFR phosphorylation, MEK1 phosphorylation, AKT phosphorylation, Ki-67 expression and/or cyclin D1 expression in intestinal polyps and normal intestinal mucosa with treatment.

4. Determine β-catenin localization in adenomatous intestinal polyps with or without oncogenic KRAS mutations.

5. Analysis using the intention to treat design.

2 BACKGROUND

Colorectal cancer (CRC) is the second leading cause of cancer deaths in the United States and in 2008 there will be an estimated 148,810 incident cases of CRC with 49,960 deaths (Jemal et al., 2008). There is strong evidence that the vast majority of colorectal cancers develop from benign dysplastic polyps termed adenomas (Leslie et al., 2002). In order to continue the current trend for decreased CRC mortality in the U.S., better prevention and treatment will be required. Elucidation of the early molecular alterations that contribute to neoplastic transformation offers specific targets for improvements in CRC prevention.

The current paradigm for colorectal tumorigenesis is the adenoma-carcinoma sequence, a process involving the acquisition of sequential mutations in multiple proto-oncogenes and tumor suppressor genes (Fearon and Vogelstein, 1990; Hahn and Weinberg, 2002; Hanahan and Weinberg, 2000). One of the earliest and commonest mutations in colorectal tumors occurs in the APC gene, a tumor suppressor that regulates cell proliferation and migration (Fodde and Brabletz, 2007). Mutational inactivation of APC leads to increased β-catenin-dependent
transcription of genes such as \textit{CCND1} (cyclin D1) and \textit{MYC}, which contribute to tumorigenesis (Sansom et al., 2007). \textit{APC} mutational inactivation also leads to β-catenin-independent decreases in retinoid synthesis, which in turn leads to increased COX-2 expression (Eisinger et al., 2006). COX-2 over-expression increases tumor cell proliferation, survival, and invasion, and increases levels of prostaglandin E$_2$, which in turn activate EGFR, AKT, and WNT signaling (Eisinger et al., 2006).

Ample data show that COX-1 and COX-2 inhibitors (aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and COX-2 selective inhibitors) can significantly reduce the risk of CRC in humans (Thun et al., 2002). Although EGFR inhibitors are important adjuncts in the treatment of CRC, only preclinical data demonstrate their efficacy as chemo-preventive agents in colorectal tumor models. The combination of the NSAID sulindac and EGFR inhibition diminished adenoma development by 87% in mice with a germline \textit{Apc} mutation (Roberts et al., 2002).

Importantly, only a low dose of sulindac was required for this combinatorial effect with EGFR inhibition. Substantiation and testing of this model in patients with germline \textit{APC} mutations may lead to greatly improved CRC chemoprevention strategies in humans. We will evaluate efficacy of the combination of COX and EGFR inhibitors on intestinal polyps in patients with FAP, because they have germline APC mutations, many adenomas, and molecular genetic alterations in their intestinal tumors that are found in many sporadic colorectal tumors.

### 2.1 Epidermal Growth Factor Receptor Expression and Significance in Cancer

The control of cell growth is mediated by a complex network of signaling pathways responsive to external influences, such as growth factors, as well as to internal controls and checks. Epidermal growth factor (EGF) was one of the first growth factors to be described. It was shown to be mitogenic, an effect mediated by the binding of EGF (or other ligands) to the cell surface EGF receptor (EGFR), stimulating autophosphorylation of the intracellular tyrosine kinase domain of the receptor. Subsequent investigations revealed EGFR to be one of a family of closely related receptors that includes EGFR (HER1), HER2, HER3, and HER4.

EGFR and other HER family members are considered to be important in the development, progression, and aggressive behavior of human epithelial malignancies and to be relevant therapeutic targets. A number of human malignancies are associated with aberrant or over-expression of EGFR (Salomon et al. 1995). Stimulation of tumor cells via the EGFR is important for both tumor growth and tumor survival in vivo. Over-expression of EGFR in certain human tumors, including non–small cell lung carcinoma (NSCLC), has been correlated with both chemo-resistance and poor prognosis (Rusch et al. 1996, 1997; Davies and Chamberlin 1996; Veale et al. 1987, 1993; Sekine et al. 1998; Pfeiffer et al. 1996; Cerny et al. 1986; IMPATH Inc 1998–1999; Reissmann et al. 1999; Fujino 1996; Fontanini et al. 1995; Lei et al. 1999). Inhibitors of EGFR tyrosine kinase activity have been in development for a number of years, and although earlier compounds lacked specificity and potency, newer compounds have proven active in nonclinical and clinical studies.

Tarceva (erlotinib; previously known as OSI-774) is an orally active, potent, selective inhibitor of the EGFR tyrosine kinase. Early clinical data with Tarceva indicate that the compound is generally safe and well tolerated at doses that provide the targeted effective concentration based on nonclinical experiments. A recently completed, randomized, double-blind, placebo-
controlled trial has shown that Tarceva as a single agent significantly improves the survival of patients with incurable Stage IIIb/IV NSCLC who have failed standard therapy for advanced or metastatic disease (Shepherd et al; Proceedings of ASCO 2004; Abst 7022).

### 2.2 Sulindac as a COX-2 inhibitor

Sulindac is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic activities in animal models. The mechanism of action, like that of other NSAIDs, is not completely understood but is related to prostaglandin synthetase inhibition. Several observational studies showed that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), through inhibition of COX-1 and COX-2 and other actions, are associated with reduced mortality from CRC by as much as 40-50% (Thun et al., 2002). COX-2 is frequently over-expressed in colorectal tumors and contributes to colorectal carcinogenesis through a number of mechanisms such as invasion, angiogenesis, and cell survival in a mouse model of FAP (Oshima et al., 1996). PGE₂ is the major COX product in colorectal tissue and is an important mediator of colorectal tumorigenicity (Eberhart and Dubois, 1995). Sulindac has been shown to induce regression of colorectal polyps in FAP patients (Giardiello et al., 1993; Labayle et al., 1991; Nugent et al., 1993; Rigau et al., 1991; Waddell et al., 1989; Waddell and Loughry, 1983). Polyp regression occurred between 1 and 12 months at total daily doses of 150 mg to 400 mg. Sustained polyp regression for 9 to 92 months has been reported with continued therapy; however, polyps recurred within 3 to 6 months in most persons who discontinued therapy. Data from small and uncontrolled studies show variable effects of sulindac on sporadic adenomatous polyps including disappearance, regression and decreased numbers (Hixson et al., 1993; Matsuhashi et al., 1997).

### 2.3 The Familial Adenomatous Polyposis Syndromes

FAP occurs in about 1 in 10,000 live births. Inheritance is autosomal dominant and in the majority (80%) of inherited cases, there is a mutation of the APC gene (Groden et al., 1991; Kinzler et al., 1991). The syndromes are characterized by few to thousands of colorectal adenomas. Polyps occur at an average age of 15 years and almost all affected persons have polyps by age 35. Colorectal cancer occurs at about age 39 and is inevitable if the colon is not removed (Burt, 1995). Attenuated FAP is a subtype of FAP and is characterized by fewer colorectal polyps (average = 40), colorectal cancer at a later age than in classic FAP, and a genotype often characterized by mutations at the 5' and 3' ends of the coding region, exon 9 or a number of other, mostly alternatively spliced regions in the APC gene (Burt et al., 2004; Leppert et al., 1990; Spirio et al., 1993). Since attenuated FAP patients have fewer colorectal adenomas than classic FAP patients, many do not require colectomy and can be managed endoscopically.

Efficacious chemoprevention for duodenal adenomas is an unmet clinical need in Familial Adenomatous Polyposis (FAP) patients that would reduce the morbidity from duodenectomy and risk of duodenal adenocarcinoma. Currently the only FDA-approved chemopreventive agent is celecoxib which results in a modest reduction of duodenal and colorectal polyps and is associated with cardiac toxicity at effective doses. If it can be shown that combinatorial inhibition of COX-2 and EGFR activity leads to successful regression in duodenal adenomatous polyps in FAP, it could be used as an effective chemopreventive regimen in FAP patients with...
duodenal adenomas or who have undergone surgical resection of duodenal adenomas or have many rectal adenomas.

### 2.4 Study Rationale

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 enhance the COX-2–EGFR axis.

Multiple studies show that while the COX inhibitor sulindac and the sulindac sulfone metabolite significantly inhibited colorectal adenomas in FAP patients, they failed to significantly reduce duodenal adenomas in the same patients. One published explanation for this disparity is that COX-2 expression is higher in the normal and adenomatous mucosa in the small intestine than in the normal and adenomatous mucosa of the large intestine in Familial Adenomatous Polyposis (FAP) patients. We hypothesize that combinatorial inhibition of COX-2 and EGFR activity will lead to successful regression in duodenal adenomatous polyps in FAP patients.

Compelling clinical reasons to test the combinatorial efficacy of COX and EGFR inhibitors on duodenal and colorectal adenomas in FAP patients are: a) efficacious chemoprevention for duodenal adenomas is an unmet clinical need in FAP patients that would reduce the morbidity from duodenectomy and risk of duodenal adenocarcinoma; and b) the only current FDA-approved chemo-preventive agent, celecoxib, results in a modest reduction in duodenal and colorectal polyps and is associated with significant cardiac toxicity at effective doses.
3. DRUG INFORMATION

3.1 Description of erlotinib (Tarceva)

Erlotinib (TARCEVA®; NDA-021743) is a kinase inhibitor indicated for

1. maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.
2. the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen and
3. first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine.

3.1.1 Formulation (and Tarceva placebo)

Tarceva oral tablets are conventional, immediate-release tablets containing erlotinib as the hydrochloride salt. In addition to the active ingredient, Tarceva contains lactose (hydrous), microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and magnesium stearate.

Tablets containing 25 mg, 100 mg, and 150 mg of Tarceva are available. The 25 mg dose will be used for this study. Astellas Pharmaceuticals will provide placebo and the 25 mg Tarceva without trade dress to the NCI for distribution to the study.

3.2 Nonclinical Data of Tarceva

3.2.1 Pharmacology

Tarceva, a quinazoline, directly and reversibly inhibits the human EGFR tyrosine kinase with an IC₅₀ of 2 nM (0.79 ng/mL) in an in vitro enzyme assay and reduces EGFR autophosphorylation in intact tumor cells with an IC₅₀ of 20 nM (7.9 ng/mL). This potent inhibition is selective for the EGFR tyrosine kinase both in assays assessing the effects of Tarceva on a variety of other isolated tyrosine kinases and in cellular bioassays designed to isolate this functional pathway. Tarceva is designed to inhibit EGF-dependent proliferation of cells at submicromolar concentrations and blocks cell cycle progression in the G1 phase.

Data on drug exposure and anti-tumor responses in human tumor xenograft models (HN5 and A431) were analyzed in order to estimate the plasma concentration of erlotinib associated with anti-tumor activity. Based on these efficacy models, the minimum steady-state plasma concentration targeted for clinical activity in humans is projected to be 500 ng/mL.

3.2.2 Toxicology

Toxicology studies have been performed in mice, rats (up to 6 months), dogs (up to 1 year), and monkeys (1 week). Treatment-related effects observed in at least one species or study included effects on the cornea (atrophy, ulceration), skin (follicular degeneration and inflammation, redness, and alopecia), ovary (atrophy), liver (necrosis), kidney (papillary necrosis and tubular dilatation), lacrimal glands (atrophy), salivary glands (atrophy), mandibular lymph nodes
3.3 Clinical Experience with Tarceva

3.3.1 Dose Selection for Single-Agent Trials of Tarceva

Phase I trials of Tarceva explored both schedule and dose to evaluate the safety, tolerability, and pharmacokinetic profile of the compound given as a single agent. A number of pharmacokinetic trials in healthy subjects have been conducted, along with three classic Phase I trials in patients with advanced cancer. The single-agent maximum tolerated dose (MTD) was estimated to be 150 mg administered once daily.

The primary toxicities of single-agent Tarceva consisted of rash (dermatosis), diarrhea, nausea, fatigue, stomatitis, vomiting, and headache. When given daily, dose-limiting toxicity (diarrhea) was observed at 200 mg/day. At 150 mg/day, diarrhea was manageable with the addition of loperamide therapy; this dose was considered the maximal tolerated dose.

Rash (variously referred to as dermatitis, acneiform rash, or maculopapular rash) has been variable in onset, duration, and severity, but typically appears on the face, neck, scalp, chest, and back starting after ~1 week of treatment. The mechanistic basis of the rash remains uncertain; histopathologic examination of biopsies of the rash demonstrated inflammatory cell infiltrate and mild epidermal hyperproliferation. In some cases, the rash gradually improved despite continued dosing and, in general, resolved without sequelae following Tarceva discontinuation. The rash did not result in study discontinuation in patients with cancer in the Phase I trials. Laboratory abnormalities observed infrequently with single-agent Tarceva involved primarily liver function tests, including elevation of ALT, AST, and/or bilirubin.

Selection of the 150 mg/day dose of Tarceva for subsequent single-agent studies was based on pharmacokinetic parameters, as well as the safety and tolerability profile of this dose in Phase I trials in heavily pretreated patients with advanced cancer. Drug levels seen in patients with cancer receiving the 150 mg/day dose were consistently above the average plasma concentration of 500 ng/mL targeted for clinical efficacy. For this chemoprevention study, a dose of 75 mg/day has been selected to reduce the occurrence of adverse events, in particular rash, which would discount the blinded aspect of the study.

3.3.2 Pharmacokinetics of Tarceva

Oral Tarceva is well absorbed and has an extended absorption phase, with mean peak plasma levels occurring at 3 hours after oral dosing of 150 mg/dL at steady state. A study in healthy subjects provided an estimate of bioavailability of 59% (95% CI: 55%, 63%). The time to reach steady-state plasma concentration was ~5 days. The accumulation ratio with daily dosing of Tarceva was estimated to be 2.0. From a population pharmacokinetic analysis of 708 patients,
the median trough concentration ($C_{\text{min}}$) 24 hours following the previous dose was $1041$ ($\pm 697$) ng/mL. Median AUC achieved during the dosing interval at steady state was $19,801$ ng$\cdot$hr/mL. Exposure after an oral dose is increased by food.

There is extensive binding of Tarceva and metabolites to both serum albumin and AAG (alpha-1-acid glycoprotein), with total plasma protein binding for Tarceva and OSI-420 (metabolite) of $\sim 95\%$ and $91\%$, respectively. Tarceva is extensively metabolized in the liver by the hepatic cytochromes in humans–primarily by CYP3A4 and to a lesser extent by CYP1A2. The primary metabolite of Tarceva, OSI-420, has potency comparable to that of erlotinib, but is present at levels that are $<10\%$ of erlotinib levels. Tarceva is excreted predominantly via the feces ($>90\%$). The elimination half-life after a 150-mg oral dose is $\sim 30$ hours. In population-based data analyses, no relationships were identified between predicted steady-state trough concentration and patient age, body weight, sex, ethnicity, or creatinine clearance.

3.3.3 Phase II and III Trials in Patients with Advanced Cancer with Tarceva

Multiple Phase II trials evaluating the safety, tolerability, and antitumor activity of Tarceva have been conducted in patients with advanced, refractory malignancies including cancer of the head and neck, lung, aerodigestive tract, ovary, breast, central nervous system (glioma), and others. Tarceva has been evaluated both as a single agent and administered concurrently with conventional chemotherapy agents using various doses and schedules.

Evidence of activity has been observed in squamous cell carcinoma of the head and neck, ovarian, breast and pancreatic carcinoma, non–small cell lung cancer (NSCLC), and glioblastoma multiforme (GBM). Patients received 150 mg/day of Tarceva in all of these studies except the GBM study where dose escalation was allowed until limited by rash and where a higher starting dose was tested in subjects receiving concomitant enzyme inducing anti-epileptic drugs. Dose reduction was allowed in all studies in the case of intolerance. Diarrhea was treated with loperamide therapy and/or dose reduction. Rash was treated with a variety of agents, including oral and topical antibiotics, corticosteroids, and other agents.

Patients receiving Tarceva in combination with various chemotherapy agents have generally experienced the same type of adverse events (AEs) as with either agent alone.

The first randomized placebo controlled trial to demonstrate a survival advantage for an EGFR inhibitor was the Phase III study, BR21. This international trial, conducted by the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG), included 731 patients with incurable Stage IIIb/IV NSCLC who have failed standard therapy for advanced or metastatic disease. Patients randomized in a 2:1 ratio to single-agent Tarceva 150 mg/day obtained a 42.5% improvement in median survival over placebo, from 4.7 to 6.7 months. The one-year survival increased significantly (from 22% to 31%) as did the median and 6 month PFS, response rate, and the time to deterioration of tumor related symptoms of pain, cough, and dyspnea. (Shepherd 2004).

In BR-21, of the 727 patients evaluable for safety (485 Tarceva, 242 placebo), the most common AEs in the Tarceva arm were rash (75% Tarceva, 17% placebo), diarrhea (54% Tarceva, 18% placebo) and stomatitis (17% Tarceva, 18% placebo) events. The majority of these events were mild to moderate in severity. The incidence of interstitial lung disease (ILD) reported was the same in the placebo and Tarceva groups at 0.8% in each arm.
Two large, Phase III, randomized studies in first-line NSCLC patients evaluated Tarceva in combination with platinum-based two-drug combination chemotherapy. A total of 1079 previously untreated patients received carboplatin/paclitaxel with either Tarceva or placebo in the TRIBUTE trial (OSI2298g) conducted in the United States. An additional 1172 patients received cisplatin/gemcitabine plus either Tarceva or placebo in the TALENT trial (BO16411) conducted in 27 countries in Europe and other ex-U.S. locations. Neither study met its primary endpoint of improved overall survival or a secondary endpoint of improved time to disease progression or overall response rate. Overall, the number of adverse events and serious adverse events were well balanced between the two arms of each study, with two exceptions. As expected, rash and diarrhea occurred more frequently in the Tarceva arms. In the TRIBUTE study, more serious adverse events resulting in death were seen in the Tarceva arm compared with the placebo arm (53 vs. 27). Most of the apparent imbalance was due to events reported as pneumonia or progression of underlying cancer. (Gatzemeier U. et al. 2007 and Herbst RS et al. 2005).

### 3.3.4 Patients with Hepatic or Renal impairment

The influence of hepatic metastases and/or hepatic dysfunction on the pharmacokinetics of Tarceva is not yet known. However, Tarceva is cleared predominately by the liver, and caution should be used when administering Tarceva to patients with hepatic dysfunction. Tarceva is also a strong inhibitor of the UDP-glucuronosyltransferase UGT1A1 enzyme responsible for the glucuronidation of bilirubin. Hyperbilirubinemia appears most often to be a side effect related to genetic polymorphisms of UGT1A1. Rare cases of hepatic failure (including fatalities) have been reported during the postmarketing use of Tarceva. Confounding factors for severe hepatic dysfunction have included pre-existing liver disease such as cirrhosis, viral hepatitis, hepatocellular carcinoma, hepatic metastases, or concomitant treatment with potentially hepatotoxic drugs.

A study comparing the pharmacokinetics of Tarceva in patients with moderately impaired hepatic function with patients with normal hepatic function showed no significant difference in exposure suggesting that no dose modification is necessary for moderately hepatic-impaired patients. Caution, however, may need to be exercised in these patients as authors of an independent study performed by a collaborative group recommended a Tarceva dose of 75 mg daily in patients with hepatic dysfunction.

Rare cases of myocardial infarction (including fatalities) have been reported during the postmarketing use of Tarceva.

No clinical studies have been conducted in patients with compromised renal function since Tarceva and its metabolites are not significantly excreted by the kidneys.

### 3.4 Description of Sulindac

Sulindac is a FDA approved drug for the treatment of arthritic conditions and available as a generic (ANDA 071897 Watson Pharmaceuticals and others). It is used “off label” for polyp prevention in FAP.

Sulindac is a non-steroidal, anti-inflammatory indene derivative designated chemically as (Z)-5-fluoro-2-methyl-1-[[p-(methylsulfinyl)phenyl]methylene]-1H-indene-3-acetic acid. It is not a
salicylate, pyrazolone or propionic acid derivative. Its empirical formula is C20H17FO3S, with a molecular weight of 356.42. Sulindac, a yellow crystalline compound, is a weak organic acid practically insoluble in water below pH 4.5, but very soluble as the sodium salt or in buffers of pH 6 or higher.

### 3.4.1 Formulation

Sulindac is available in 150 and 200 mg tablets for oral administration. Each tablet contains the following inactive ingredients: microcrystalline cellulose, magnesium stearate, stearic acid, and starch (corn).

Following absorption, sulindac undergoes two major biotransformations: reversible reduction to the sulfide metabolite, and irreversible oxidation to the sulfone metabolite. Available evidence indicates that the biological activity resides with the sulfide metabolite.

### 3.5 Clinical Experience with Sulindac

#### 3.5.1 Pharmacokinetics of Sulindac

**Distribution:** Sulindac, and its sulfone and sulfide metabolites, are 93.1, 95.4, and 97.9% bound to plasma proteins, predominantly to albumin. Plasma protein binding measured over a concentration range (0.5-2.0 μg/mL) was constant. Following an oral, radiolabeled dose of sulindac in rats, concentrations of radiolabel in red blood cells were about 10% of those in plasma. Sulindac penetrates the blood-brain and placental barriers. Concentrations in brain did not exceed 4% of those in plasma. Plasma concentrations in the placenta and in the fetus were less than 25% and 5% respectively, of systemic plasma concentrations. Sulindac is excreted in rat milk; concentrations in milk were 10 to 20% of those levels in plasma. It is not known if sulindac is excreted in human milk.

**Metabolism:** Sulindac undergoes two major biotransformations of its sulfoxide moiety: oxidation to the inactive sulfone and reduction to the pharmacologically active sulfide. The latter is readily reversible in animals and in man. These metabolites are present as unchanged compounds in plasma and principally as glucuronide conjugates in human urine and bile. A dihydroxydihydro analog has also been identified as a minor metabolite in human urine. With the twice-a-day dosage regimen, plasma concentrations of sulindac and its two metabolites accumulate: mean concentration over a dosage interval at steady state relative to the first dose averages 1.5 and 2.5 times higher, respectively, for sulindac and its active sulfide metabolite.

Sulindac and its sulfone metabolite undergo extensive enterohepatic circulation relative to the sulfide metabolite in animals. Studies in man have also demonstrated that recirculation of the parent drug sulindac and its sulfone metabolite is more extensive than that of the active sulfide metabolite. The active sulfide metabolite accounts for less than six percent of the total intestinal exposure to sulindac and its metabolites. Biochemical as well as pharmacological evidence indicates that the activity of sulindac resides in its sulfide metabolite. An in-vitro assay for inhibition of cyclooxygenase activity exhibited an EC50 of 0.02 μM for sulindac sulfide. In-vivo models of inflammation indicate that activity is more highly correlated with concentrations of the metabolite than with parent drug concentrations.
Elimination: Approximately 50% of the administered dose of sulindac is excreted in the urine with the conjugated sulfone metabolite accounting for the major portion. Less than 1% of the administered dose of sulindac appears in the urine as the sulfide metabolite. Approximately 25% is found in the feces, primarily as the sulfone and sulfide metabolites.

The mean effective half-life ($T_{1/2}$) is 7.8 and 16.4 hours, respectively, for sulindac and its active sulfide metabolite. Because sulindac is excreted in the urine primarily as biologically inactive forms, it may possibly affect renal function to a lesser extent than other non-steroidal anti-inflammatory drugs; however, renal adverse experiences have been reported with sulindac.

In healthy men, the average fecal blood loss, measured over a two-week period during administration of 400 mg per day of sulindac, was similar to that for placebo, and was statistically significantly less than that resulting from 4800 mg per day of aspirin.

3.5.2 Patients with Hepatic or Renal impairment

Patients with acute and chronic hepatic disease may require reduced doses of sulindac compared to patients with normal hepatic function since hepatic metabolism is an important elimination pathway. Following a single dose, plasma concentrations of the active sulfide metabolite have been reported to be higher in patients with alcoholic liver disease compared to healthy normal subjects. Accordingly, patients with hepatic impairment will not be enrolled in this trial.

Sulindac pharmacokinetics have been investigated in patients with renal insufficiency. The disposition of sulindac was studied in end-stage renal disease patients requiring hemodialysis. Plasma concentrations of sulindac and its sulfone metabolite were comparable to those of normal healthy volunteers whereas concentrations of the active sulfide metabolite were significantly reduced. Plasma protein binding was reduced and the AUC of the unbound sulfide metabolite was about half that in healthy subjects. Sulindac and its metabolites are not significantly removed from the blood in patients undergoing hemodialysis. Since sulindac is eliminated primarily by the kidneys, patients with significantly impaired renal function will not be enrolled in this trial.

3.6 Over-encapsulated sulindac tablets (Blinding of drugs)

HCI investigational pharmacy will encapsulate the sulindac and matching placebo. Their state of Utah Division of Occupational & Professional Licensing (DOPL) license numbers are 5646774-1704 (Pharmacy-Class B); 5646774-8913 (Dispensing Controlled Substance License); 5646799-1703 (Pharmacy – Class A); and 5646799-8913 (Dispensing Controlled Substance License). HCI’s Investigational Pharmacist working with this study is Rian Davis. His DOPL license numbers 6102666-1701 (Pharmacist) and 6102666-8911 (Pharmacist Controlled Substance). HCI’s investigational pharmacy will use a ProFill 100 capsule filling machine. Capsules will be purchased from CapsuleWorld.com. The 150 mg sulindac tablets will be encapsulated in approximately “000” size capsule (large) with the addition of starch (corn). Identical capsules for placebo B will be filled with starch (corn). Pharmacy-grade starch (corn) will be purchased from Medisca, Inc.
3.7 Risks and Known Adverse Reactions

3.7.1 Risks from sulindac
Common side effects (> 3% of people) are gastrointestinal pain, dyspepsia, nausea, diarrhea, vomiting, constipation, rash, dizziness, and headache. Rare but serious side effects are risk of cardiovascular thrombotic events, myocardial infarction and stroke, congestive heart failure and edema, hypertension, serious gastrointestinal bleeding, ulceration, and perforation, cholestatic hepatitis, renal papillary necrosis, exfoliative dermatitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis and hypersensitivity to drug including anaphylaxis. This drug is Pregnancy Category C and should not be given to pregnant women.

Please refer to the sulindac product label for a comprehensive list of risks and observed adverse events.

3.7.2 Risks from erlotinib
Common side effects (≥1% and <10% of people) are rash*, diarrhea*, anorexia*, fatigue*, dyspnea, cough, nausea*, acne, anorexia, infection, vomiting, stomatitis, puritus, dry skin, conjunctivitis, keratoconjunctivitis sicca, and abdominal pain, infection, edema, pyrexia, constipation, bone pain, abnormal liver function test, epitaxis, hair and nail changes, GI bleeding (*indicates the most common side effects). Uncommon side effect (< 1% of people) includes abnormal eyelash growth. Rare but serious side effects are interstitial lung disease-like (ILD) events, renal failure, hepatotoxicity, gastrointestinal perforation, bullous and exfoliative skin disorders, myocardial infarction/ischemia, cerebrovascular accidents, microangiopathic hemolytic anemia with thrombocytopenia, ocular disorders (corneal perforation and ulceration) and hypersensitivity to drug including anaphylaxis. This drug is Pregnancy Category D and should not be given to pregnant women.

Please refer to the Tarceva product label for a comprehensive list of incidences of AEs and SAEs.

3.7.3 Risks from colonoscopy
Colonoscopy complications are rare. Bleeding may occur at the site of biopsy or polypectomy and is usually minor and self-limited, or can be controlled through the colonoscope. In rare instances, a perforation, or tear, in the intestinal wall or infection can occur. These complications may require hospitalization and, rarely, surgery. The incidence of serious complications during colonoscopy is less than 1 in 2,000 cases.

3.7.4 Risks from upper endoscopy
A temporary, mild throat irritation sometimes occurs after the exam. Due to the sedation, the patient should not drive or operate machinery following the exam. Serious risks are very uncommon (less than 1 per 4,000 procedures). One such risk is excessive bleeding (especially with removal of a large polyp) and infection. In extremely rare instances, a perforation, or tear, in the intestinal wall can occur. These complications may require hospitalization and, rarely, surgery. Biopsy of the ampulla of Vater in the duodenum carries a slight risk for pancreatitis. In
cases where biopsy of the ampulla is required, biopsies will be obtained away from the ductal opening.

### 3.7.5 Other risks

Obtaining blood samples may cause some discomfort, bruising, bleeding from the site of sampling, formation of a blood clot, and, in rare cases, infection.

## 4 STAGING CRITERIA

Not applicable

## 5 ELIGIBILITY CRITERIA

### 5.1 Inclusion Criteria

Patients must fulfill all of the following criteria to be eligible for study enrollment:

1. Patients who are 18 years to 69 years at time of enrollment with a clinical or genetic diagnosis of FAP or attenuated AFAP.
2. Presence of duodenal polyps with a sum of diameters ≥ 5mm.
3. Minimum of two weeks since any major surgery.
4. WHO performance status ≤ 1
5. Adequate bone marrow function as shown by: normal leukocyte count, platelet count ≥ 120 x 10^9/L, Hgb > 12 g/dL
6. Adequate liver function as shown by: normal serum bilirubin (≤ 1.5 ULN) and serum transaminases (≤ 2.0 ULN)
7. Patient must discontinue taking any NSAIDS within one month of treatment initiation.
8. Patients must be able to provide written informed consent.

### 5.2 Exclusion Criteria

Patients meeting any of the following criteria are ineligible for study entry:

1. Prior treatment with any investigational drug within the preceding 4 weeks.
2. Malignancies within the past 3 years except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin.
3. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study as determined by the Principle Investigator such as:
   a. Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months prior to first study treatment, serious uncontrolled cardiac arrhythmia
   b. Severely impaired lung function
   c. Any active (acute or chronic) or uncontrolled infection/disorders.
   d. Nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with the study therapy
Liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis

4. Screening clinical laboratory values that indicate any of the following:
   a. anemia
   b. thrombocytopenia
   c. leucopenia
d. elevations of transaminases >2X ULN
e. elevation of bilirubin > 1.5 X ULN
f. alkaline phosphatase elevation > 1.5 X ULN
g. increased creatinine, urinary protein, or urinary casts outside the clinically normal range.

5. Gastrointestinal bleeding (symptoms including dyspnea, fatigue, angina, weakness, malaise, melena, hematochezia, hematemesis, anemia or abdominal pain will require clinical assessment to rule out gastrointestinal bleeding).

6. Patient who is currently taking any anti-coagulation medication.

7. Women who are pregnant or breast feeding.

8. Patients with a known hypersensitivity to sulindac or erlotinib or to their excipients

6 Stratification Factors
Not applicable

7 Treatment Plan
This will be a single-center, phase-II, six-month-long, placebo-controlled, double blinded, randomized trial of the EGFR inhibitor erlotinib (Tarceva) and the COX inhibitor sulindac in patients with FAP or attenuated FAP to test the following hypothesis: The combination of COX and EGFR inhibitors will cause a significant regression of duodenal adenomas in FAP and attenuated FAP patients. This is an intention to treat design.

100 patients with FAP or attenuated FAP will undergo a 6-month placebo-controlled, randomized duodenal adenoma regression study with sulindac 150 mg twice daily + erlotinib 75 mg once daily. Only patients with duodenal polyps with a sum of diameters ≥ 5mm will be enrolled (see Appendix A for flow chart). We designed this trial to be six months so that polyps will likely be present for analysis for the secondary aims. In a period of six months, we predict that polyps will be reduced, but not gone.

Patients will be randomly assigned to treatment or placebo arms. Randomization will be performed by the IDS pharmacist using a random number table, stratified between FAP and attenuated FAP groups. A total of 50 patients will be recruited to each arm. Numbers will be computer-generated in blocks of 4 or less. The Chair of the Data and Safety Monitoring Committee (DSMC) will have access to the list of subject names, agent code, and identity. A sealed envelope containing the drug identity will be maintained in the subject’s study file in case a clinical emergency requires immediate information. Opening of this envelope will cause the subject to be dropped from the study.
7.1 Administration Schedule

7.1.1 Dosage, Administration, and Storage

Tarceva will be provided in 25 mg doses along with an identical placebo A. Sulindac will be encapsulated in 150 mg doses along with an identical encapsulated placebo B. Both drugs/placebo will be self-administered in a blinded fashion in all patients enrolled in the study. During the treatment period, patients will receive 3 capsules of Tarceva at 75 mg/day or 3 capsules of placebo A and 2 capsules of Sulindac at 300 mg/day or placebo B. Tarceva/placebo should be taken at the same time each day with 200 mL of water at least 1 hour before or 2 hours after a meal. One capsule of Sulindac/placebo B will be taken twice per day with meals (breakfast and supper).

Suppliers: Sulindac will be purchased from the Huntsman Cancer Hospital Pharmacy from Watson Pharmaceuticals (ANDA#071891; NDC#000591-5661-01). Erlotinib and an identical-looking placebo A will be provided by Astellas Pharmaceuticals, Inc (NDA#021743; NDC#50242-062-01) through the NIH. Sulindac and placebos will be over-encapsulated so that patients and physicians will be blinded to treatment.

Packaging and Labels: Drug inserts for each drug will be supplied and discussed with the patients.

Storage: The study medication will be stored at room temperature, protected from environmental extremes and in a locked cabinet or room.

Dispensing: The Investigational Drug Studies Pharmacist will be responsible for dispensation to the subjects and will have access to the drug code. There will be 2 groups consisting of approximately 50 subjects each. Following determination of eligibility, each subject will be given a unique subject number and thereby be assigned to a group.

Drug Accountability: The Investigational Drug Studies Pharmacist will maintain adequate records of the receipt, dispensing, and final disposition of the study drug. The receipt record will include from whom the study drug was shipped, date, quantity, and batch or lot number. The dispensing record will note the quantities and dates the study drug was dispensed to and returned by each patient. At the completion of the investigation, all unused study drug will be returned to the Huntsman Cancer Hospital Pharmacy (Rian Davis, pharmacist) to be counted and destroyed. The record documenting the return of unused drug should include the quantity, date, batch or code, and name of the person or department to whom the drug was returned.

Dose Reduction: Dose reductions for adverse events will be permitted (see Section 8.2). Treatment is continued daily until a reason for termination of study therapy is identified (see Section 8.4).

8 TOXICITIES AND DOSEAGE MODIFICATION

8.1 General Plan to Manage Safety Concerns

For all endoscopy procedures, only highly skilled gastroenterologists are used. For blood drawing, only skilled technicians are used. Patients will have monthly coordinator contact and...
physician visits at 0, 3 and 6 months for toxicity and evaluation of their general health while enrolled in the study. The study staff will be in regular contact and available on call to respond to any adverse reactions that the participants may have. A dose modification plan for expected and unexpected adverse events is in place and described below.

A number of measures will be taken to ensure the safety of patients participating in this trial, addressed through exclusion criteria and routine monitoring. Patients will be evaluated for adverse events at each study visit for the duration of their participation in the study and for 30 days after the discontinuation of treatment.

Skin toxicities will be monitored by routine physical examination and managed symptomatically. The following agents may be used to treat rash: alcohol-free emollient cream, diphenhydramine, topical or oral corticosteroids, and topical (clindamycin) or oral antibiotics (tetracycline, minocycline, doxycycline). Topical drying agents are not recommended. Bullous, blistering and exfoliative skin conditions have also been reported. Tarceva treatment should be interrupted or discontinued if the patient develops severe exfoliative skin symptoms.

Diarrhea will be monitored and managed symptomatically. Guidelines for management include administration of loperamide and Tarceva dose reduction/interruption as described in Section 8.2 and Table 2.

Although quite rare, interstitial lung disease (ILD) can be life threatening. Therefore, patients should be monitored closely for symptoms consistent with ILD, such as new onset dyspnea without an obvious cause. In the event that ILD is suspected, Tarceva treatment should be discontinued and the patient should receive appropriate medical management. Although there is no proven therapy, systemic corticosteroids are often provided. Tarceva should not be restarted in those patients suspected of having drug-related ILD. See Section 8.2 and Table 2 for management guidelines, including Tarceva dose interruption.

Liver function abnormalities, including elevated serum ALT, AST, and/or bilirubin, have been observed infrequently with single-agent Tarceva and occasionally with Tarceva in combination with concomitant chemotherapy. Periodic monitoring of liver function is recommended. Tarceva dosing should be interrupted if changes in liver function are severe.

Gastrointestinal perforation have been reported in patients receiving Tarceva. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxan-based chemotherapy, or who have a prior history of peptic ulceration or diverticular disease are at an increased risk. Tarceva treatment should be discontinued in patients who develop gastrointestinal perforation.

Corneal perforation or ulceration have been reported during Tarceva use. Other ocular disorders observed include abnormal eyelash growth, keratoconjunctivitis sicca, or dermatitis, and are known risk factors for corneal ulceration/perforation. Tarceva treatment should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain.

Since both study drugs are Pregnancy Category C or D, the following precautions will be taken: A serum ß-human chorionic gonadotropin (ß-HCG) will be performed initially on all fertile women, then monthly for the first 3 months then at 6 months. Contraception or abstinence will be required of all fertile female enrollees and will be continuously verified during scheduled follow-up phone calls and clinic visits.
8.2 Dose Modifications

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 Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov).

Dose reduction or interruption of Tarceva/Placebo A or Sulindac/Placebo B for toxicity may take place at any time during the study. Toxicity grading is based on NCI-CTCAE, v 4.0. Dose level reductions are presented in Table 1. If patients do not tolerate the second Tarceva dose reduction or first Sulindac reduction, treatment is to be discontinued.

<p>| Table 1 |
| Dose Level Reductions |
|---|---|---|</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose a</th>
<th>First Reduction</th>
<th>Second Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tarceva</td>
<td>75 mg/day</td>
<td>50 mg/day</td>
<td>25 mg/day</td>
</tr>
<tr>
<td>Sulindac</td>
<td>300 mg/day</td>
<td>150 mg/day</td>
<td>NA</td>
</tr>
</tbody>
</table>

Tarceva specific toxicities:

Management of a tolerable Grade 2 or 3 rash should include continuation of Tarceva 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 patients requiring dose reduction for skin toxicity. Patients experiencing Grade 4 skin toxicity should be discontinued from study treatment.

For Grade 1 or 2 diarrhea, early intervention should include continuation of Tarceva 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. Patients experiencing Grade 3 diarrhea should interrupt Tarceva until resolution to Grade ≤1 and re-start at a reduced dose according to Table 2. Patients should be maintained at the reduced dose without attempt at dose re-escalation. Patients experiencing Grade 4 diarrhea should be discontinued from study treatment.

Tarceva should not be restarted in those suspected of having drug-related interstitial lung disease (ILD).
Table 2  
Dosage Modification Criteria and Guidelines for Management  
of Tarceva-Related Toxicities

<table>
<thead>
<tr>
<th>NCI-CTCAE (v 4.0) Grade</th>
<th>Tarceva Dose Modification</th>
<th>Guideline for Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>None</td>
<td>Consider loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until free of diarrhea for 12 hours)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>None</td>
<td>Loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until diarrhea free for 12 hours)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Interrupt then dose reduce Tarceva. Tarceva should not be re-escalated.</td>
<td>Interrupt Tarceva until resolution to Grade ≤ 1, and restart at next reduced dose</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue study treatment.</td>
<td>Manage as described above</td>
</tr>
</tbody>
</table>

**Pulmonary Events if possibly ILD**

| All Grades | Temporarily interrupt Tarceva pending the diagnostic evaluation. If the pulmonary adverse event is assessed as related to Tarceva, discontinue the patient 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 |

**Sulindac specific toxicities:**

Findings of anemia, thrombocytopenia, leucopenia, elevations of transaminases greater than 2 X normal, elevation of bilirubin > 1.5 X normal, alkaline phosphatase elevation > 1.5 X normal, increased creatinine, urinary protein, or urinary casts are found, the investigators will have the study coordinators contact the patient and schedule the patient for another set of laboratory
studies to verify the results within 7 days. If the abnormalities are verified and felt to be tolerable and not a serious threat to the safety and health of the patient, then the investigators will decrease the dosage of the drugs (decrease erlotinib to 50 mg daily and sulindac to 150 mg daily). If the adverse events are felt to endanger the patients’ health, the study medications will be discontinued. If the laboratory values are felt to be life threatening or serious, the patient will be instructed to stop the study medications and be taken to the nearest emergency medical facility for urgent evaluation.

Any clinical evidence of gastrointestinal bleeding (new symptoms including dyspnea, fatigue, angina, weakness, malaise, melena, hematochezia, hematemesis; laboratory findings – anemia) or new symptoms including abdominal pain will result in temporary discontinuation of study drug and rapid clinical assessment. If clinical assessment finds patients are OK, study drug will be continued. If gastrointestinal bleeding is confirmed, treatment will be discontinued and all necessary medical care will be provided.

**Table 3**

<table>
<thead>
<tr>
<th>NCI-CTCAE (v 4.0) Grade</th>
<th>Dose Modification</th>
<th>Guideline for Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anemia or Liver function problems (Lab values)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 &amp; 2</td>
<td>Decrease Tarceva to 50 mg and Sulindac to 150 mg daily.</td>
<td>Monitor lab values weekly</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Discontinue study treatment</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue study treatment</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1-4</td>
<td>Discontinue study treatment.</td>
<td>Manage as described above</td>
</tr>
</tbody>
</table>

For any patients being taken off study due to a SAE, the blind will be broken for those cases and the study investigators and DSMC members will then determine if the adverse event was related to the study medications.

**Un-blinding:**

The master study code will be maintained by the Rian Davis at the Huntsman Cancer Hospital Pharmacy. Access to the code will be available to the Chair of the DSMC. The code may be broken for medical emergencies or untoward serious adverse events. This would be done in consultation with the Committee Chair, the NCI-Program Director. The identity of the treatment to which a subject is assigned will be contained in an opaque, sealed envelope, labeled with the patient’s study number. The code may be broken only if an emergency situation arises that in the investigator’s opinion requires knowledge of the code. The date and reason for breaking the code will be submitted to the DSMC Chair, NCI contact and U of Utah IRB by the investigator along with the opened envelope. Any patients for whom the envelope seal has been broken will be excluded from the data analysis but will be noted as an adverse event.
8.3 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

8.4 Duration of Therapy

Patients may discontinue study treatment at any time. Any patient who discontinues treatment will be encouraged to return to the study center to undergo treatment discontinuation assessments. The primary reason for discontinuation should be recorded. Reasons for discontinuation of a patient by the investigator include, but are not limited to, the following:

- Clinically significant deterioration of the patient’s condition prior to treatment discontinuation.
- Adverse events: the patient develops an adverse event, which in the opinion of the patient or Investigator warrants termination from the study. Persistent (≥3 weeks) NCI-CTCAE version 4.0 Grade 3 or Grade 4 adverse event or any significant adverse event that compromises the patient’s ability to participate in the study.
- Personal reason: a patient may withdraw at any time.
- Non-compliance: the patient was inappropriately enrolled or fails to comply with instructions concerning drug administration (misses 70% of doses for 3 consecutive assessments) or clinic visits.
- Lost to follow up: diligent attempts will be made by telephone and letter to determine the circumstances for loss to follow up since such loss may be related to the study drug.
- Investigator determination that it is not in the patient’s best interest to continue participation.
- Pregnancy.
- The NCI may request that the treatment of a particular patient be discontinued.

When a subject discontinues use of the study drug the following should be performed:

- Reason for discontinuation will be determined and recorded in patient’s file.
- If reasonable, a clinic visit for history and physical exam, and if reasonable, to obtain upper and lower endoscopies (if intact colon or rectal stump).
- Appropriate management of adverse events including notification of NCI monitor, DSMC, and IRB (U of Utah).
- Review of supplemental medications, compliance assessment, and return of unused medications.
- CBC, blood chemistry studies, and urine analysis.

9 STUDY CALENDAR

The study will cover screening esophagogastroduodenoscopy (EGD) and colonoscopy; these will be performed in the Center for Clinical Translational Science at University of Utah. All study specific procedures will be covered by the study. This includes all of the clinical laboratory tests, the pregnancy tests, and the EGD and colonoscopy done at 6 months. The drugs will also be provided by the study. If a medical condition is discovered any time during the screening, enrollment, or treatment phase, the participant will be responsible for tests, procedures, and costs incurred for this medical condition outside of the study. For example, if a polyp is discovered
during screening endoscopy that will require surgery, they will be referred to clinical care outside of the study.

9.1 Screening and Pretreatment Assessments

Recruitment. Patients will be recruited through the Clinical Core C of the PPG which includes the Hereditary Gastrointestinal Cancer Registry at Huntsman Cancer Institute (IRB# 30546), past research participants from IRBs 14000 and 5829, clinical referral, and the trial will be posted on clinicaltrials.gov and HCI web sites.

Screening Procedures:

Following informed consent for the study, patients will undergo: an educational session explaining the study, major endpoints, and potential risks involved; a history and physical examination; and, baseline laboratory studies done (see Table 4 for study calendar). They will receive contact information for reaching study personnel during and after regular work hours. A pregnancy test will be performed on all fertile women. Contraception will be required of all fertile female enrollees and will be continuously verified during scheduled follow-up phone calls and pregnancy test will be repeated monthly for the first 3 months then at 6 months. They will then be scheduled for upper and lower gastrointestinal endoscopies.

Gastrointestinal Regions Studied. Informed consent will be obtained prior to and before each procedure. Patients will be monitored (blood pressure, heart rate, pulse oxygenation) and then sedated with intravenous fentanyl and propofol or other sedative at the discretion of the treating physician. Glucagon is sometimes administered intravenous to reduce small bowel motility. Esophagogastroduodenoscopy (EGD) will be performed and a tattoo placed 10 cm distal to the pyloric channel to define a region heretofore referred to as the duodenal segment, which will extend from the pyloric channel distally to the tattoo. When possible, video will be captured for the 10cm duodenal segment and available for review before and after treatment.

Colonoscopy or sigmoidoscopy will be used to examine the entire large intestine/colon in attenuated FAP patients with intact colons (over half of our attenuated FAP patients have intact colons) and the rectal stump in FAP or attenuated FAP patients who have undergone colectomy. For consistency, those with a rectum or rectal stump, biopsies of normal tissue will only be done if 15 cm of rectum (from the anal verge) is present. When possible, video will be captured and available for review before and after treatment.

Pre-treatment Endoscopic Assessment. Topical lidocaine may be used for pharyngeal anesthesia at the physicians discretion. Conscious sedation will be administered by the endoscopist-investigator, as is the current clinical standard of practice. Medicines will primarily consist of propofol and fentanyl, but other sedatives are occasionally needed. Endoscopy will be performed in the standard fashion. A side-viewing endoscope will be used as needed specifically to examine and record the size of the ampulla of Vater in the duodenum. 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 on a form, which has been used extensively in polyp studies at this institution. Estimates of the polyp sizes will be
performed using a bendable endoscopic measuring device (M2-3U; Olympus Optical Co., Ltd., Tokyo, Japan) with 1-mm increment markings. Each polyp in the duodenal segment will be measured, mapped, and recorded at 1-cm intervals in the 10-cm segment. In the colon and rectum, each polyp within the right colon (cecum to and including the hepatic flexure), transverse colon (transverse colon to splenic flexure), left colon (splenic flexure to rectum) and rectum will be measured and recorded.

During both endoscopic procedures, polyps ≥ 10 mm in diameter will be biopsied from the 10-cm duodenal segment and removed if possible, colon (attenuated FAP) and rectal stump (FAP & attenuated FAP) and sent to the Clinical Core C for histological analysis. The 10mm diameter threshold was chosen since polyps 5-10mm in diameter have only a 0.9% chance of harboring cancer (Butterly et al., 2006) thus reducing the chances that polyps progress to high grade dysplasia or cancer during the 6-month trial. 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. Biopsies of normal tissue will be taken from the duodenum and colon. These will be used for patient matched pre- and post-treatment as well as comparing the molecular phenotype of individuals with (randomized on trial drugs) and without (excluded) duodenal polyps. Patients whose duodenum is carpeted with polyps will be excluded from the study and referred to surgery for management.

Once screening is complete, patients either A) fulfill all eligibility criteria and are enrolled or B) do not fulfill all eligibility criteria and are screened out.

9.2 Evaluations and Procedures During Treatment

Randomization and Treatment. The patients will be randomized to receive: 1) erlotinib 75 mg orally once per day + sulindac 150 mg orally twice per day or 2) placebos.

On-Treatment Assessments. During the treatment phase, patients will be contacted every two weeks for the first three months, then monthly by the study coordinator to ensure compliance with medications (they will be asked to keep a study diary), use of birth control, update changes in concomitant medications, and review of side effects (especially weakness, fatigue, rash, diarrhea, stomatitis, abdominal pain, melena, hematochezia, nausea, vomiting). The NCI Common Toxicity Grading Scale version 4.0 will be employed to specify toxicities and an external DSMC comprised of four colon cancer experts and a statistician who are not co-investigators or consultants on this proposal will oversee the study data. The study coordinators will review any side effects with the study physicians who will then determine the appropriate follow-up of the patients. Any new medications will be noted and reviewed by the study physicians as soon as they are noted. Patients will also be asked to call if these or other side-effects occur.

The study physicians will be responsible for reviewing the monthly laboratory studies and performing appropriate evaluations, dose reduction, and discontinuation of the drugs if adverse events are felt to be possibly related to the study medications. The patients will have labs obtained monthly for the first 3 months and at month 6 and will undergo a clinic visit with the study physicians at the beginning of the study and then at 3 and 6 months. Out of town study patients may schedule their month 3 clinic visit (physical exam and safety labs) with their local Primary Care Provider so as to avoid an additional trip back to SLC. Necessary month 3 study
follow up parameters and requirements will be communicated by the study coordinator to the patient’s provider prior to scheduled visit. Clinical exam notes/results will be returned to study for review by study physician. A history and physical will be performed and labs will be reviewed with the patient. The following clinical lab evaluations will be monitored during the treatment phase to monitor for adverse events of the medications: Urinalysis, CBC (complete blood count), chemistry profile (Na, K, Cl, CO2, BUN, creat, glu, Ca, AST, ALT, Alk Phos, TBili, urate) and pregnancy test in females. These will be performed/completed by University of Utah staff, the patients’ local clinical care facility, or contracted with a professional phlebotomy service adhering to all HIPAA regulations (eg. Phlebotomy Services International Inc).

**TABLE 4 – Schedule and timetable of study events for each patient**

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Baseline/Screening</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Month 4</th>
<th>Month 5</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical/Surgical History</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician Visit/Physical Exam</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Vital Signs (blood pressure)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Upper &amp; Lower GI Endoscopies</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Serum Pregnancy Test (female)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Hematology</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Chemistry (Comprehensive Metabolic Panel)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Pt. Contact to Query for AEs, Concomitant Medications and Study Compliance - Every 2 Weeks for 1st 3 months, then monthly</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dispense Drug/Drug Accountability</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**End-of-Treatment Endoscopy.** At the end of the 6-month treatment period (+14 or -14 days) or if patient withdraws from study and it is reasonable to obtain an endpoint, all visible polyps will be counted, measured, and recorded as performed in the pretreatment endoscopies. When possible, a video will be taken of the 10 cm portion of the duodenum and the colon. A side-viewing endoscope will be used as needed to examine and measure the ampulla of vater. Again, biopsies of the ampulla will only be obtained if it is enlarged or appears suspicious for malignancy. We will attempt the removal of polyps in the duodenal segment and colon/rectal stump in all study patients based on medical judgment. If the polyps are deemed to large or numerous to be safely removed by the endoscopist, then the patients will be referred for surgical therapy.

Polyps removed because of medical judgment will be sent to Core C (clinical) for histopathological evaluation. Four (2 largest and 2 smallest) confirmed adenomas will be sent from the pathology laboratory in Core C to the research laboratory in Core B for immunohistochemical analysis. If available and not needed for histopathological evaluation, four polyps (6-9mm X 2 and 2-5mm X 2) removed from the duodenal segment and colon/rectal stump will be sent to Core B for RNA extraction. Normal biopsies will be obtained from the duodenal segment and/or colon.
Using the service of Core C (clinical), histopathological examination will be performed on tissue from the polyps. Polyp specimens will be processed for microscopic examination by standard methods. The finding of high grade dysplasia or cancer will result in a referral to a surgeon for clinical management.

### 9.3 Follow-Up Assessments

Patients 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 laboratory values are found at the end of the study (6-month time point), these will be repeated at 30 days. If all lab values are normal, no additional laboratory tests will be done.

### 10 Safety and Monitoring

The DSMC will monitor data concerning safety, recruitment, retention, and adherence after 20 patients have undergone treatment for at least three months, and roughly every 6 months thereafter. In addition to these data, the DSMC will also review efficacy data concerning the primary endpoint and other secondary outcomes at two interim analyses scheduled after the primary outcome has been determined in 1/3 and 2/3 of the study participants. The timing of the safety, recruitment, retention and adherence analyses will be adjusted as necessary to coincide with the two formal interim analyses for efficacy. The DSMC may recommend termination of the trial due to early demonstration of efficacy, safety concerns, or problematic data concerning recruitment, retention or adherence indicating that the study will not be able to accomplish its scientific objectives.

#### 10.1 Interim Analyses of Efficacy

Two formal interim analyses for demonstration of efficacy will be performed after the primary outcome has been ascertained for 1/3 and after 2/3 of the 100 targeted evaluable patients using an O’Brien-Fleming early stopping boundary (stop early if you show exceptional benefit or harm) to preserve a studywise Type I error of 5%.

There is no formal early stopping criterion based on futility. However, a conditional power analysis will be provided to the DSMC at the two efficacy interim analyses.

#### 10.2 Safety

The DSMC will periodically review (see schedule above) detailed summaries of data concerning adverse events as described in Section 15.5, including the frequencies of persistent (> 3 weeks) NCI-CTCAE version 3.0 Grade 3 or Grade 4 adverse events or any significant adverse events that compromises participation in the study.
10.3 Adherence

Cumulative non-compliance will be defined for each patient as the percent of all follow-up prescribed doses which are missed, and “current” noncompliance will be summarized as the percent of missed doses over the patient’s last three assessments or visits. The distribution of cumulative and current non-compliance will be periodically reviewed by the DSMC (see schedule described above). The DSMC may recommend corrective action or termination of the study in the event of excessive noncompliance. As a benchmark, compliance will be viewed as potentially problematic for study power if more than 25% of patients have > 50% noncompliance.

10.4 Measurement of Effect

The primary endpoint will be 1) a comparison of the total adenomatous polyp burden in the duodenum, measured as the change ΔD in the sum if the diameters of the adenomatous polyps from the duodenal segment. At the end of the 6-month treatment period, all visible polyps will be counted, measured, and recorded as performed in the pretreatment endoscopies. The primary analysis will be via Wilcoxon (Mann-Whitney) tests comparing the sulindac + erlotinib and placebo arms.

Expected Results: Based on preclinical trials showing efficacy of EGFR inhibition in adenoma progression in animal models of FAP (Roberts et al, 2002; Torrance et al, 2000) and the studies from the previous funding period, we expect a significant regression of duodenal segment and colonic/rectal adenomas in patients treated with sulindac and erlotinib. In preclinical models of FAP, genetic and pharmacological inhibition of EGFR signaling along with low doses of sulindac resulted in a 97% reduction in intestinal adenomas (Roberts et al, 2002; Torrance et al, 2000).

Secondary Endpoint 1: Change in duodenal polyposis based on Spigelman classification (stages 0-IV) which is based on polyp number, size, histology and severity of dysplasia. A comparison of Spigelman classification in the duodenum based on the table below will be assigned before and after treatment. Separate analyses of the Spigelman classification and the number of Spigelman points will be performed using the Wilcoxon (Mann-Whitney) test.

<table>
<thead>
<tr>
<th>Spigelman classification for duodenal polyposis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Polyp number</td>
</tr>
<tr>
<td>Polyp size (mm)</td>
</tr>
<tr>
<td>Histology</td>
</tr>
<tr>
<td>Dysplasia</td>
</tr>
</tbody>
</table>

Stage 0, 0 points; stage I, 1-4 points; stage II, 5-6 points; stage III, 7-8 points; stage IV, 9-12 points. Points are accumulated for polyps’ number, size, histology and severity of dysplasia. Stage I (1-4 points) indicates mild disease, whereas stage III-IV (7-12 points) implies severe duodenal polyposis.
Expected Results: We expect a significant reduction in Spigelman classification and total Spigelman points with patients treated with erlotinib and sulindac parallel to the primary endpoint.

Secondary Endpoint 2: A comparison of the total adenomatous polyp burden in the duodenum, measured as the change ΔC in the sum of the diameters of the colorectal polyps in subjects with an intact colon and choosing to undergo colonoscopy. At the end of the 6-month treatment period, all visible polyps will be counted, measured, and recorded as performed in the pretreatment endoscopies. The primary analysis will be via Wilcoxon (Mann-Whitney) tests comparing the sulindac + erlotinib and placebo arms.

Expected Results: Based on preclinical trials showing efficacy of EGFR inhibition in adenoma progression in animal models of FAP (Roberts et al, 2002; Torrance et al, 2000) and the studies from the previous funding period, we expect a significant regression of colonic/rectal adenomas in patients treated with sulindac and erlotinib. In preclinical models of FAP, genetic and pharmacological inhibition of EGFR signaling along with low doses of sulindac resulted in a 97% reduction in intestinal adenomas (Roberts et al, 2002; Torrance et al, 2000).

Secondary Endpoint 3: Change in COX-2 expression, EGFR phosphorylation, MEK1 phosphorylation, AKT phosphorylation, Ki-67 expression and/or cyclin D1 expression in intestinal polyps and normal intestinal mucosa. (See section 15.1.2 for assay details)

Expected Results: If sulindac + erlotinib treatment results in significantly lower levels of EGFR phosphorylation, AKT phosphorylation, and cyclin D1 expression in the normal, and adenomatous tissues compared with placebo, it will indicate that the combination of sulindac and erlotinib diminish EGFR activation and signaling. The cell cycle progression marker, Ki-67, will be used as a readout of cellular proliferation. Since EGFR signaling has been shown to induce COX-2 expression, we expect that COX-2 protein and RNA levels will be significantly decreased in the normal and adenomatous tissue samples in the treatment arm compared with placebo.

Secondary Endpoint 4: Determination of β-catenin localization in adenomatous intestinal polyps with or without oncogenic KRAS mutations. (See section 15.2.1 for assay details)

Expected Results: We expect to find a correlation between oncogenic KRAS mutations and nuclear β-catenin localization in intestinal adenomas from FAP/attenuated FAP patients. This would be important information since the studies performed in the previous funding period suggests that APC mutation alone is insufficient for nuclear β-catenin localization, which is infrequently observed in intestinal ACFs and adenomas in FAP patients.

11 POWER ESTIMATES FOR PRIMARY OBJECTIVE

Primary Efficacy Analysis

The primary aim is to determine if the combination of sulindac and erlotinib causes a significant regression of duodenal in FAP and attenuated FAP patients. The primary analysis will be via Wilcoxon (Mann-Whitney) tests comparing the sulindac + erlotinib and placebo arms.

Determination of Sample Size
A total of ~200 patients with FAP or attenuated FAP will be recruited to undergo upper gastrointestinal endoscopy. Patients with a sum of duodenal polyps totaling 5 mm or more will be enrolled, as duodenal polyps will be our chief endpoint. Based on recruitment rates of 74% in a previous familial polyposis study, with a similar cohort of patients, we estimate that of 208 patients recruited, that 154 will enroll the study. Based on results of a previous clinical trial we have conducted (DiSario et al., in preparation) in which 65% of FAP and attenuated FAP patients were found to have duodenal polyps, we anticipate that 100 patients will undergo study treatment (50 placebo; 50 study drugs).

<table>
<thead>
<tr>
<th>Sample size per group (N)</th>
<th>Reduction in the sum of polyp diameters (ΔD) in the treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25%</td>
</tr>
<tr>
<td>30</td>
<td>67%</td>
</tr>
<tr>
<td>35</td>
<td>74%</td>
</tr>
<tr>
<td>40</td>
<td>79%</td>
</tr>
<tr>
<td>45</td>
<td>84%</td>
</tr>
<tr>
<td>50</td>
<td>87%</td>
</tr>
</tbody>
</table>

### 12 DISCIPLINE REVIEW

Not applicable

### 13 REGISTRATION GUIDELINES

Once patients have undergone all screening tests and procedures and found to fulfill eligibility requirements listed in section 5, they may be registered and enrolled. An enrollment form along with the signature page on the informed consent is received by the study pharmacist, Rian Davis. Patients must not start protocol treatment prior to registration. Patients should start treatment within 30 days of randomization.

### 14 DATA SUBMISSION SCHEDULE

The CRFs (Case Report Forms) are a set of forms for each patient that provides a record of the data generated according to the protocol. These forms will be completed on an on-going basis during the study. The medical chart will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail. The CRF will be retained in locked filing cabinets at the Huntsman Cancer Institute. The CRFs will
be completed by the Study Coordinator or Investigator. The data will be reviewed annually by the Data and Safety Monitoring Committee. The Investigator will allow the DSMC personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

15 SPECIAL INSTRUCTIONS

15.1 Correlative Studies

15.1.1 Specimen Submission

At the end of the treatment phase:

1. Normal intestinal mucosa and 3 polyps removed by biopsy from the duodenum as well as colon/rectum will be placed in RNA-Later for RNA extraction and COX-2 mRNA levels determined by quantitative RT-PCR.

2. Normal intestinal mucosa and 3 confirmed adenomas removed by biopsy from the duodenum as well as colon/rectum (if present) will be frozen and used for immunohistochemical detection of phosphorylated EGFR, AKT, COX-2, β-catenin, Ki-67, and cyclin D1.

15.1.2 Assay Methods

Immunohistochemical analysis of intestinal tissue:

Using the service of Core C (clinical), histopathological examination will be performed on tissue from the polyps. Polyp specimens will be processed for microscopic examination by standard methods. The finding of high grade dysplasia or cancer will result in a referral to a surgeon for clinical management.

Change in COX-2 expression, EGFR phosphorylation, MEK1 phosphorylation, AKT phosphorylation, Ki-67 expression and/or cyclin D1 expression in intestinal polyps and normal intestinal mucosa.

Sections of normal tissue and visible polyps will be processed by the Analytic Core B for immunohistochemical detection of phospho-EGFR, phospho-AKT, phospho-MEK1 and Ki-67 and/or cyclin D1 protein expression, all of which would indicate EGFR signaling. A single GI pathologist, who is blinded to the treatments, will measure the ratio of stained cells based on the J-scoring system (J0 is no stained cells; J1 is ≥ 1% stained cells; J2 is 1%< >10% stained cells; J3 ≤ 10% stained cells (Allred, et al, 1998; Kurosumi, et al 2007) and the intensity of staining (0, 1+, 2+) for each protein. Ordinal logistic regression will be used to analyze immunohistochemical endpoints. Changes in COX-2 mRNA expression will be determined by quantitative RT-PCR of mRNA isolated from normal, and adenomatous intestinal tissues. We will use normal linear models to assess the combined effects of treatment arm, size, location (duodenum, colon/rectum), mutation (attenuated FAP versus FAP), gender, and age on qRT-PCR outcomes.
Determination of β-catenin localization in adenomatous intestinal polyps with or without oncogenic KRAS mutations.

Our preliminary data shows that KRAS mutation or activation of wild-type KRAS may be required in addition to APC mutation for nuclear localization of β-catenin in early adenomas. After the treatment phase, four duodenal and colon/rectal (if colon or rectum is present) adenomas (2 largest and 2 smallest from each area) from each patient will be immunostained for β-catenin localization and graded by a pathologist, who is blinded to treatment status, for nuclear β-catenin (none, weak, present). A colorectal cancer specimen with nuclear β-catenin and normal intestinal mucosa without nuclear β-catenin will be used as positive and negative controls, respectively.

Fifty adenomas of the total obtained, each from the duodenal segment and colorectum showing no or positive nuclear β-catenin will undergo micro-dissection of adenomatous tissue for DNA extraction (Samowitz et al., 2000). KRAS from this DNA will be amplified by PCR and sequenced to look for oncogenic hotspot mutations. Oncogenic KRAS mutations and nuclear β-catenin localization will be correlated. Ordinal logistic regression will be used to analyze immunohistochemical endpoints.

15.2 Informed consent

Informed consent will be obtained from all research participants prior to participation. (See ICF).

15.3 Institutional Review

Study will be approved by the Institutional Review Board of University of Utah.

15.4 Data Monitoring and Safety Plan

An external Data and Safety Monitoring Committee (DSMC) is established as required and charged with reviewing study progress, patient accrual, data management, and patient safety, and to cooperate on the publication of results. The DSMC will document progress in written reports to the NCI Program Director, and will provide periodic supplementary reports to designated NCI staff upon request. The DSMC will be comprised of external, non-participating consultant-investigators with expertise in FAP, gastrointestinal oncology, pharmacology, clinical and fundamental studies. The voting members of the DSMC will include: David Weinberg, M.D., M.Sc., Professor and Chairman, Department of Medicine, Fox Chase Cancer Center, Paul Limburg, M.D. (Chair of DSMC), M.P.H., Associate Professor of Medicine, Mayo Clinic, William M. Grady, M.D., Assoc. Professor of Medicine, Chief GI, Fred Hutchinson Cancer Center, Sonia Kupfer, M.D., Assistant Professor of Medicine University of Chicago Medical Center and Richard Holubkov, Ph.D., Professor, University of Utah Department of Pediatrics, Pediatrics Chief Biostatistician. The DSMC will initially meet during the start up phase of the study. The structure of the DSMC will be established and a Chair elected. The Principal Investigator will attend the initial meeting but will not be a member or routine attendee of the DSMC thereafter. The DSMC will meet again in the first year of the study and at least yearly thereafter. The Chair is responsible for coordinating the DSMC activities, for preparing meeting agendas, and for scheduling and chairing meetings. The Chair will have access to the
randomization codes, and will be notified of all serious toxicities and may call an immediate committee meeting or defer the DSMC review until the next regularly scheduled meeting.

Rian Davis, Pharm. D. will oversee study medications and will have randomization data in order to take care of adverse events.

Rian Davis, Pharm. D.
Huntsman Cancer Hospital, Suite 2110
1950 Circle of Hope
Salt Lake City, UT 84112
(801) 585-0272 phone

The Investigator will allow the DSMC personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities. All data generated by the study will be managed at the Huntsman Cancer Institute. The Study Coordinator and Research Assistant will enter data and perform periodic checks for errors. Dr. John Valentine will be the designated quality control investigator and will be responsible for documenting accurate and timely assessment of study progress.

John Valentine, MD
Professor of Medicine Department of Medicine
University of Utah Gastroenterology Division
30 North 1900 East
SOM 4R118
Salt Lake City, UT 84132-2410
Office Phone: (801) 5878275
Office Fax: (801)
E-mail: john.valentine@hsc.utah.edu

Dr. Valentine has extensive experience with treating patients with inflammatory bowel disease and he is developing laboratory research and clinical trials in ulcerative colitis and Crohn’s disease in order to expand the understanding and treatment options for patients with these diseases. Dr. Valentine is well qualified to perform in the capacity of quality control investigator. Quality control topics to be reviewed include subject accrual, protocol compliance, treatment and follow-up, laboratory data, endoscopy reports, pathology reports, apoptosis assays, and data integrity. Random cross checks will be performed under the direction of Dr. Valentine, Study Group chaired by the Project Leader, and comprised of all the Utah-based personnel will meet quarterly to review the progress of the study and coordinate all efforts. This group will review immunohistochemical staining and quantitative RT-PCR results for consistency and quality.

Huntsman Cancer Institute’s Data Safety and Monitoring Committee will have access to the study DSMC minutes, and Dr. Valentine’s evaluations.

**15.5 Adverse Events**

All adverse events will be reported to the DSMC and University of Utah IRB. Details of the timeline in reporting adverse events are included in this section. If the patient suffers a serious
adverse reaction to the medication the participant will be taken off therapy and referred for proper medical care as described in section 8 of this protocol.

15.5.1 Safety assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry, and regular measurement of vital signs, namely blood pressure, and the performance of physical examinations.

These assessments should be performed within ±7 days of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study. Safety and tolerability will be assessed according to the NIH/NCI CTCAE v4.0

http://ctep.cancer.gov/forms/

15.5.2 Definition of Adverse Event (AE)

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade (mild to severe based on CTCAE version 4.0) or (grade 1-4)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes a serious adverse event (SAE)

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.
Information about common side effects already known about the investigational drug is described in the Drug Information section 3 and can be found in the FDA-approved product labels. This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

15.5.3 Definition of Serious Adverse Event (SAE)

Serious adverse events

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

• is fatal or life-threatening
• results in persistent or significant disability/incapacity
• requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  o routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
  o elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  o treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  o social reasons and respite care in the absence of any deterioration in the patient’s general condition
  o is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

15.5.4 Recording of AE / SAE

ADR REPORTING FOR COMMERCIAL DRUGS - PHASE II
(No IND drugs utilized in treatment)

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 Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov)

Commercial Agents: Sulindac (NDA 071891 Watson Pharmaceutical) and erlotinib (NDA-021743 Astellas Pharmaceuticals)

All adverse events will be noted on an Adverse Reaction Case Report Form whether or not they are felt to be related to the study drug. A quarterly report of all adverse reactions will be submitted to Dr. Hagedorn, the DSMC, and U. Utah’s IRB.
The following adverse reactions must be reported to HCI Data and Safety Monitoring Committee, NCI, study sponsor and the IRB in the manner described below. Toxicities occurring on this arm should be considered investigational.

<table>
<thead>
<tr>
<th></th>
<th>Grade 2-3 unexpected</th>
<th>Grade 4 unexpected</th>
<th>Death due to Rx or within 30 days of Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report SAE to NCI/DCP Medical Monitor within 24 hours</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>SAE Form to NCI/DCP Medical Monitor within 48 hours</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>SAE Form to DSMC within 10 days</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Notify local IRB within 10 days</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

1 Any unexpected toxicity not reported in the literature or the package insert must be reported.

2 Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended but which is felt to be treatment related, must be reported.

**Serious Adverse Event Reporting to NCI**

In the interest of patient safety in this study and to fulfill regulatory requirements, serious adverse events (no matter the apparent relationship to study medication) will be reported to the IRB, NCI and DSMC.

Any serious adverse event, including any event resulting in death, which occurs during the study, will be reported by telephone, fax, or email within 24 hours of the Investigator learning of the event to the assigned DCP Medical Monitor.

DCP Medical Monitor
Marjorie Perloff MD
mp114e@nih.gov
Chemoprevention Branch
DCP/National Cancer Institute/NIH
Executive Plaza North, Suite 201
9000 Rockville Pike
Bethesda, MD 20892

A written report will follow within 48 hours of the event to the assigned DCP Medical Monitor. Besides the initial 24-hour telephone report, all serious adverse events must be entered in the Adverse Reaction CRF. Prompt follow up of the clinical outcome will be sent to the NCI. The Project Leader will give written notification to the IRB within 10 working days of all serious or unexpected adverse events.
Follow-up plan for adverse events. All adverse events, including laboratory abnormalities that in the opinion of the Investigator are adverse events, will be followed up according to good medical practices. If a trigger point is reached, the Investigator will discuss the issue with the NCI Staff Collaborator and DSMC.

Non-Treatment Related Toxicities

Toxicities which fall within the definitions listed above must be reported as a SAE regardless if they are felt to be treatment related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above, must simply be clearly documented on the HCI flow sheets which are submitted to the HCI Clinical Trials Office.

15.6 Protocol amendments, or changes in study conduct

All amendments including administrative must be approved by the IRB. These requirements for approval should in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

A Protocol Deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the Institutional Review Board (IRB). Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events. Any changes in the research protocol during the period, for which the IRB approval has already been given, may not be initiated without submission of an amendment for IRB review and approval. Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below.

A subset of protocol deviations must to be reported to the IRB. The IRB requires the prompt reporting of protocol deviations which are:

- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

15.7 FDA Annual Reporting

N/A – IND exempt (IND acknowledgement #108086)

15.8 Clinical Trials Data Bank

The study is registered on http://clinicaltrials.gov
16 BIBLIOGRAPHY


Protocol name: Genetic Events Leading to APC-Dependent Colon Cancer in High-Risk Families; a clinical trial of COX and EGFR inhibition in familial polyposis patients.
Version Date: December 15, 2014
Principal Investigator: N. Jewel Samadder, MD


17 MASTER FORM SET
Case Report Forms will be created for study.

18 APPENDIX
18.1 APPENDIX A: Study Flowchart

Flowchart detailing sequence of procedures, eligibility criteria, 2-arm strategy and biopsy plan for the proposed clinical trial

AFAP and FAP patients

Upper GI and Lower GI Endoscopy

< 5 mm sum diameter duodenal polyps

Placebos

≥ 5 mm sum diameter duodenal polyps

Erlotinib and Sulindac

6 months

Upper GI and Lower GI Endoscopy

Remove polyps in duodenal segment and colon/rectum

Upper GI Primary Endpoint
Duodenal Segment Polyps

Secondary Endpoints
Duodenal & Rectal Polyps
Tissue Molecular Markers
Colon and rectal polyps
18.2 Appendix B: List of CYP3A4 Inhibitors

From http://www.georgetown.edu/departments/pharmacology/davetab.html

The following are known inhibitors of CYP3A4:

- Delavirdine
- Nelfinavir
- Saquinavir
- Cimetidine
- Clarithromycin
- Diltiazem
- Fluconazole
- Gestodene++
- Itraconazole
- Mifepristone
- Norfloxacin
- Mibefradil
- Atazanavir
- Telithromycin

- Indinavir
- Ritonavir
- Amiodarone
- Ciprofloxacin
- Diethyl-dithiocarbamate
- Erythromycin
- Fluvoxamine
- Grapefruit juice
- Ketoconazole
- Nefazodone
- Norfluoxetine
- Troleandomycin
- Indinavir
- Voriconazole

The following are known inducers of CYP3A4:

- Rifampicin
- Rifabutin
- Carbamazepine
- St. John’s Wort

- Phenytoin
- Rifapentine
- Phenobarbital
18.3 APPENDIX C: Description of Clinical Core C and Analytic Core B of the Program Project Grant

18.3.1 CORE C: CLINICAL REGISTRY CORE

Rationale and Core Functions

The Clinical Registry Core (Core C) has been established for over two decades with the purpose of supporting human high-risk colon cancer investigations at the University of Utah. Core C provides a comprehensive long-term resource for clinical and basic science investigations, including clinical trials, and at the same time provides for clinical care of involved persons and families who have an inherited risk of colon cancer. The core provides the projects of this PPG with necessary resources for: 1) gene discovery, clinical characterization and interventional research, 2) systematic bio-specimen collection for genetic and molecular studies, and 3) computerized data management of both patient care and research information. This core serves as a pivotal resource for each of the program investigations and is a vital point of interaction between research subjects, clinical investigators, basic scientists, and information managers. Core C allows research to be translational, in that genetic and laboratory findings will be appropriately applied to disease prevention in individuals under study.

There are several main components coordinated by the Core C infrastructure: 1) referring high-risk colon cancer clinics, including: the Familial Cancer Assessment Clinic, the Familial Colon Cancer Study, and the Familial Polyposis Study, 2) the Familial Colon Cancer Registry, a registry of patients with inherited or familial colon cancer; 3) the Subject Database, a customized software package and database used to support high-risk cancer investigations, and 4) the Utah Population Database, an electronic linkage of extensive genealogies, medical records (including the Utah Cancer Registry, a SEER resource), and statewide vital statistics.

During the previous funding period, Core C (formerly known as the Familial Colon Cancer Clinics and Registry) matured into a fully functional and productive research and clinical care program. It earned respect from its scientific peers nationally and internationally, as well as from the clinical care community locally, regionally, nationally, and internationally. Recently, this resource has been extended on a limited basis to both US and international colleagues.

Huntsman Cancer Institute, which houses Core C, funds this infrastructure in large part; support funds also come from the budgets of specific investigations. The clinics of this core are staffed by investigator physicians, nurses, coordinators, genetic counselors, and computer professionals.

Integral functions of Core C are:

- Maintenance of a large data base registry of syndromic and nonsyndromic high-risk colon polyp and cancer persons and families. All registry subjects have agreed to be contacted when studies become available for possible study inclusion.

- Identification and expansion of high-risk colon cancer persons and kindreds to support investigator-initiated studies, including: subject contact; study registration; administration of informed consent; demographic, epidemiological, medical, and family cancer history collection.
- Acquisition, maintenance, and assembly of cohorts of biospecimens for studies; including management and tracking of data
- Electronic integration and tracking of patient medical histories, genealogies, physical samples, patient interactions, and genetic and molecular testing information
- Clinical investigation and care, including:
  - Education, genetic counseling, and testing
  - Cancer and polyp screening and surveillance: upper GI endoscopy, colonoscopy or sigmoidoscopy for polyp and cancer diagnosis and tissue sampling
  - Assistance with clinical trials planning, development and execution (See Project 1 for in depth description of this aspect of Project 1 of the Program)
- Treatment and follow-up, appropriate patient referral for indicated therapies
- Maintenance of strict confidentiality

### 18.3.2 CORE B: Analytical Services Core

Analytic Core B provides support for a “systems biology” approach to understanding colorectal cancer. This approach includes coordinating tissue collection, processing and distribution. In addition, the Analytic Core performs a variety of molecular morphological analyses including routine histology, immunohistochemistry, in situ hybridization, laser capture microdissection, RT-PCR, digital photography. The core also facilitates the study of genes that may underlie the molecular pathways that lead to colon cancer using zebrafish as a functional genomics model system. Core B offers three main services: (1) collection and storage of human colon tissue specimens; (2) characterization of human and murine colon tissues and (3) examination of relevant genes in zebrafish intestinal development. Each service is summarized below.

#### 1. Collection of Human Colon Tissue Specimens.
Analytical Core B works with the Huntsman Cancer Institute Tissue Research and Application Core and Core C to provide centralized collection and distribution of tissues taken during colonoscopy or from surgical resections performed at participating hospitals. Informed consent is obtained prospectively for both groups of subjects. Each collected tissue specimen is assigned a unique identifier before being divided into three samples: fresh, frozen, and fixed. Fresh samples are delivered for immediate use by program project investigators as needed. Other samples from the same specimen are snap-frozen in liquid nitrogen and stored at 140°C until requested. In most cases, a portion of the specimens are fixed in formalin and processed through paraffin wax, and/or placed in OCT compound and frozen, and stored until analysis. A biospecimen tracking database (BST) was developed in the previous funding period and is maintained to include specimen information obtained from Core C or the surgical pathology report that accompanies each specimen.

#### 2. Characterization of Human and Murine Colon Tissues.
To maximize utilization of reagents derived from tissue specimens and to create uniform reagents, Analytical Core B isolates DNAs and RNAs from normal colon, colon adenomas, and colon carcinomas taken from either humans or mice. This core stores and distributes RNA and DNA at the request of the project leaders. In addition, the core generates and maintains cDNA libraries from RNA taken from colon tumors, polyps and normal tissue. This ensures long-term availability of genetic material from each sample and direct comparison of results among the same specimens by the
different research projects. In addition, we provide assistance to investigators in immunohistochemical and *in situ* hybridization experiments by providing the required molecular reagents and assisting with protocols. The paraffin embedded and/or OCT embedded tissue blocks are used for both purposes. Core personnel have the microtomy, molecular biology and photomicroscopy expertise and equipment to accomplish the stated objectives. Mice are used by some of the program project investigators. Core B assists these investigators by processing mouse colons in a manner analogous to the handling of human tissues. The core offers experience with routine histology, quantitative histology and immunohistochemistry using mice as experimental animal models.

3. *Zebrafish Functional Genomics Resource*. The zebrafish gastrointestinal tract displays many features similar to that of higher vertebrates. It is feasible to directly modulate gene function through genetic mutations or antisense morpholinos during early development to rapidly examine the effects of genetic perturbations on intestinal cell differentiation. Adult and embryonic tissues can be readily visualized by standard immunostaining and *in situ* hybridization techniques. Furthermore, tissues can be harvested for isolation of protein, DNA and mRNA. As such, the zebrafish represents a tractable model system for quickly manipulating and identifying specific signaling pathways required for enterocyte differentiation. In view of the attributes of zebrafish as a model system, Core B provides gene manipulation services either though overexpression or morpholino knock down to support our systems biology effort and to efficiently examine genetic pathways of intestinal differentiation.
### 18.4 APPENDIX D: WHO Performance Status Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about &gt;50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to a bed or chair &gt;50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>