Preliminary Communication

Effect of Sulindac and Erlotinib vs Placebo on Duodenal Neoplasia in Familial Adenomatous Polyposis
A Randomized Clinical Trial

N. Jewel Samadder, MD, MS; Deborah W. Neklason, PhD; Kenneth M. Boucher, PhD; Kathryn R. Byrne, MD; Priyanka Kanth, MD; Wade Samowitz, MD; David Jones, PhD; Sean V. Tavtigian, PhD; Michelle W. Done, BS; Therese Berry, BS; Kory Jasperson, MS; Lisa Pappas, MS; Laurel Smith, BS; Danielle Sample, MPH; Rian Davis, PharmD; Matthew K. Topham, MD; Patrick Lynch, MD; Elena Strait, MS; Wendy McKinnon, MS; Randall W. Burt, MD; Scott K. Kuwada, MD

IMPORTANCE Patients with familial adenomatous polyposis (FAP) are at markedly increased risk for duodenal polyps and cancer. Surgical and endoscopic management of duodenal neoplasia is difficult and chemoprevention has not been successful.

OBJECTIVE To evaluate the effect of a combination of sulindac and erlotinib on duodenal adenoma regression in patients with FAP.

DESIGN, SETTING, AND PARTICIPANTS Double-blind, randomized, placebo-controlled trial, enrolling 92 participants with FAP, conducted from July 2010 through June 2014 at Huntsman Cancer Institute in Salt Lake City, Utah.

INTERVENTIONS Participants with FAP were randomized to sulindac (150 mg) twice daily and erlotinib (75 mg) daily (n = 46) vs placebo (n = 46) for 6 months.

MAIN OUTCOMES AND MEASURES The total number and diameter of polyps in the proximal duodenum were mapped at baseline and 6 months. The primary outcome was change in total polyp burden at 6 months. Polyp burden was calculated as the sum of the diameters of polyps. The secondary outcomes were change in total duodenal polyp count, change in duodenal polyp burden or count stratified by genotype and initial polyp burden, and percentage of change from baseline in duodenal polyp burden.

RESULTS Ninety-two participants (mean age, 41 years [range, 24-55]; women, 56 [61%]) were randomized when the trial was stopped by the external data and safety monitoring board because the second preplanned interim analysis met the prespecified stopping rule for superiority. Grade 1 and 2 adverse events were more common in the sulindac-erlotinib group, with an acne-like rash observed in 87% of participants receiving treatment and 20% of participants receiving placebo ($P < .001$). Only 2 participants experienced grade 3 adverse events.

Outcome	Baseline	6-mo Follow-up	Median Change	Between-Group Difference (95% CI)	*P* Value
Median Duodenal Polyp Burden, mm					
Sulindac-erlotinib	29.0	19.5	−8.5	−19.0 (−32.0 to −10.9)	<.001
Placebo	23.0	31.0	8.0		
Median Duodenal Polyp Count, No.					
Sulindac-erlotinib	13.5	10.0	−2.8	−8.0 (−12.2 to −4.7)	<.001
Placebo	10.5	17.0	4.3		

CONCLUSIONS AND RELEVANCE Among participants with FAP, the use of sulindac and erlotinib compared with placebo resulted in a lower duodenal polyp burden after 6 months. Adverse events may limit the use of these medications at the doses used in this study. Further research is necessary to evaluate these preliminary findings in a larger study population with longer follow-up to determine whether the observed effects will result in improved clinical outcomes.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT 01187901

JAMA. 2016;315(12):1266-1275. doi:10.1001/jama.2016.2522

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com and CME Questions page 1282

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Deborah W. Neklason, PhD, High Risk Cancer Research Program, Huntsman Cancer Institute, University of Utah, 2000 Circle of Hope, Salt Lake City, UT 84112-5550 (deb.neklason@hci.utah.edu).

Familial adenomatous polyposis (FAP) is an autosomal dominant, inherited disorder caused by germline mutations in the adenomatous polyposis coli (*APC*) gene.[1] The disease is characterized by the formation of hundreds to thousands of adenomatous polyps in the colorectum and a nearly 100% lifetime risk of colorectal cancer, if left untreated.[2] Prophylactic colectomy has become the standard of care, once the extent of colorectal polyposis is beyond endoscopic control and abrogates the risk of colorectal cancer. Patients with FAP are also at greatly increased risk for duodenal neoplasia, with duodenal adenomas eventually forming in more than 50% of participants and duodenal adenocarcinoma occurring in up to 12%.[2,3] Following colectomy, duodenal adenocarcinoma is the leading cause of cancer death in these patients, and prevention of duodenal adenocarcinomas by endoscopic surveillance with polyp resection, duodenectomy, Whipple surgical procedure, and ampullectomy are often challenging and suboptimal.[4]

Multiple studies have shown that the cyclooxygenase (COX) inhibitor, sulindac (a nonsteroidal anti-inflammatory drug [NSAID]) significantly inhibits colorectal adenomatous polyps in patients with FAP[5,6]; however, NSAIDs have much less efficacy in duodenal adenomas.[7,8] Celecoxib use resulted in a modest reduction of duodenal[9] and colorectal polyps,[10,11] but is no longer US Food and Drug Administration (FDA)–approved for this indication, due to lack of complete follow-up studies.[12]

Studies have suggested that *APC* inactivation and epidermal growth factor receptor (EGFR) signaling promote cyclooxygenase 2 (COX-2) expression and the subsequent development of intestinal neoplasia.[13,14] The convergence between the *Wnt* and EGFR signaling pathways and COX-2 activity was demonstrated in a mouse model of FAP, in which a combination of sulindac and an EGFR inhibitor diminished small intestinal adenoma development by 87%.[15] These results led us to test the hypothesis that a combination of COX and EGFR inhibition would reduce adenoma formation in the duodenum of patients with FAP.

Methods

Study Design and Participants

The study was a double-blind, randomized, placebo-controlled trial of participants with FAP conducted at a single academic cancer center from July 2010 to June 2014 (**Figure 1**). Participants were identified and recruited from Huntsman Cancer Institute research registries.

Participants provided written informed consent to participate in the study, and ethical approval was obtained from the University of Utah institutional review board. The study protocol and statistical analysis plan are available in Supplement 1.

Eligible participants were aged 18 to 69 years at time of enrollment and either were proven carriers of a pathologic mutation of the *APC* gene (genetic diagnosis) or had more than 100 adenomas in the large intestine and were members of a family with FAP (clinical diagnosis). Participants with attenuated FAP and an *APC* genetic diagnosis were included. Randomized participants were required to have the presence of duodenal polyps with a minimum sum of diameters of 5 mm or more at baseline.

Exclusion criteria included the following: unwillingness to discontinue taking NSAIDs within 1 month of treatment initiation, absence of the use of effective birth control in women of childbearing age, pregnancy or breastfeeding, a white blood cell count of less than 4000/μL, a platelet count of less than 100×10^3/μL, a hemoglobin level of less than 12 g/dL, a serum creatinine level of more than 1.5 mg/dL (to convert to μmol/L, multiply by 88.4), transaminases/bilirubin/alkaline phosphatase elevations 1.5- to 2-fold above the upper limit of normal, symptoms or features of active gastrointestinal bleeding, history of allergy or hypersensitivity to sulindac, erlotinib, or its excipients, history of cancer within the past 3 years (except for adequately treated carcinoma of the cervix or basal/squamous cell carcinoma of the skin), unstable cardiorespiratory condition, active uncontrolled infection, liver disease (such as cirrhosis), active or chronic hepatitis, or prior treatment with an investigational drug within the preceding 4 weeks.

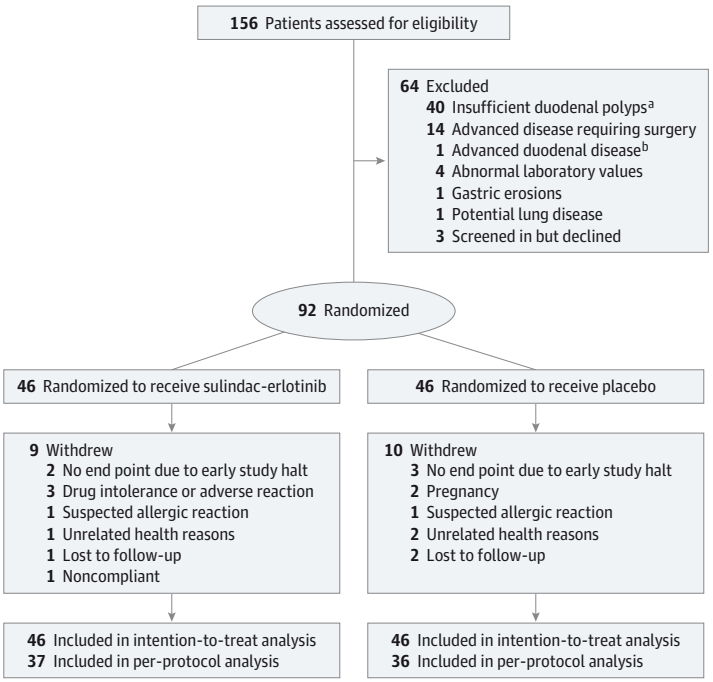
Randomization and Study Intervention

Participants were randomly assigned with an equal probability in a uniform 1:1 allocation ratio. Separate randomization tables were created using a computer program for participants with classic and attenuated FAP. The randomization was done in blocks of 2 or 4. Upon enrollment, each participant was assigned a randomization number that corresponded to a treatment on a randomization list available only to the unblinded study pharmacist. Participants were randomly assigned to receive combination therapy with sulindac at a dose of 150 mg twice daily and erlotinib at a dose of 75 mg per day or identically appearing placebo for 6 months. Erlotinib (FDA IND exemption 108086) and identically appearing placebo tablets were provided by the National Cancer Institute's Division of Cancer Prevention, through a contract with the drug manufacturer. Huntsman Cancer Institute Investigational Pharmacy provided encapsulated sulindac and identically appearing placebo capsules filled with corn starch or microcrystalline cellulose. The investigators and participants were blinded to study group assignments. After endoscopic examination at study entry to determine eligibility, study drugs were provided to participants and refilled at 1- to 3-month intervals based on scheduled study visits. Drug compliance was assessed by pill count review of participant diaries.

Primary Outcome

The burden of duodenal adenomatous polyps was assessed by endoscopy with flexible video endoscopes. Endoscopic evaluations were performed within 30 days before treatment initiation with sulindac-erlotinib or placebo was begun (month 0) and 6 months after treatment was initiated (month 6). At each examination, 1 of 4 experienced endoscopists counted and mapped the total number and size of all polyps to the nearest millimeter in a 10-cm segment of the

Figure 1. Flow Diagram of Participants Through the Study



[a] Insufficient duodenal polyps refers to a less than 5-mm sum of diameters at baseline endoscopy.

[b] Advanced duodenal disease refers to 1 patient with a greater than 1-cm duodenal polyp that was not amenable to endoscopic removal. The patient was referred to an experienced endoscopist.

duodenum measured from the first portion of the duodenum to a tattoo placed at 10 cm distal to the first portion of the duodenum at the baseline endoscopy. Multiple passes with the endoscope were made to achieve optimal polyp assessments. Each polyp in the duodenal segment was measured once. The primary end point was change in total polyp burden at 6 months. Polyp burden was calculated as the sum of the diameters of polyps and was determined at baseline and following 6 months of treatment.

Secondary Outcomes

Eleven secondary efficacy end points included (1) change in duodenal polyp number, (2) percentage of change from baseline in duodenal polyp burden, (3 and 4) duodenal polyp burden stratified by attenuated or classic FAP genotype, (5 and 6) polyp burden stratified by low vs high initial polyp burden, (7) per-protocol change in duodenal polyp burden, (8) duodenal polyp burden in the subset of participants with a genetic diagnosis, (9 and 10) duodenal polyp number stratified by attenuated or classic FAP genotype, and (11) duodenal polyp number in the subset of participants with a genetic diagnosis.

Evaluation of Safety

Participants were instructed to contact the study team if there were any changes in health. Safety was monitored by telephone interview every 2 weeks for the first 3 months, then monthly, with specific review of adverse events. Adverse event documentation included date reported, date of onset, description, toxicity grading, action taken, and physician review and assessment (if it was an expected adverse reaction, related to study drug, or conferred a change in risk). Regular telephone interviews were conducted and documented until resolution of the event. Physical examination was done at baseline and months 3 and 6 of treatment, and measurement of vital signs and clinical laboratory values were done at baseline and months 1, 2, 3, and 6. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 4.0, from the US Department of Health and Human Services.

Measurement of EGFR Activation Status

Polyps frozen in liquid nitrogen at the time of biopsy were dounce homogenized in lysis buffer (Cell Signaling Technology #9803), incubated on ice for 10 minutes, and then centrifuged at 12 000 g for 10 minutes. Protein concentrations were determined (Pierce #23225) and then 50 µg of cell lysates were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis. The levels of phosphorylated tyrosine (Tyr1148) in EGFR (Cell Signaling Technology #4404), total EGFR (Epitomics #1902), and actin (MP Biomedicals #0869100) were detected by Western blotting according to manufacturer's guidelines.

Statistical Analysis

A sample size of 50 participants in each treatment group (total, 100 participants) was calculated to provide the study with 95% power with a 2-sided α of .05 to detect a 30% reduction in the sum of polyp diameters in the treatment group from a mean of 53.0 mm to a mean of 37.1 mm. Two planned interim analyses were taken into account in these calculations. A 2-sided nominal *P* value of less than .05 for the final analysis of the primary outcome was regarded as statistically significant to account for the 2 interim analyses.

The Mann-Whitney *U* test was used to compare the 2 groups according to an intention-to-treat (ITT) principle for the primary and secondary efficacy end points. A per-protocol analysis was also performed and included all participants who had an endoscopy 6 months after initiating treatment.

Bootstrap sampling was used to create multiple imputation estimates for the 19 participants missing end point duodenal polyp burden and polyp count (9 missing in the treatment group and 10 missing in the placebo group). For each bootstrap sample, missing values were imputed based on linear regression prediction adjusted for randomized treatment group, baseline demographics (age, sex, height, weight, and classic or attenuated FAP classification) and baseline endoscopy results (baseline duodenal burden, total number of duodenal polyps, total gastric polyps, and largest duodenal polyp). Hodges-Lehmann estimates of net difference and Mann-Whitney *U* statistics were calculated for each sample. Percentile bootstrap confidence intervals were calculated for the Hodges-Lehmann estimator. The bootstrap Mann-Whitney *U* statistics, adjusted to have mean 0 under the null hypothesis, and bootstrap standard error were used to compute a *z* score. Separate bootstrap samples were run for each subgroup to create equal treatment groups and subgroups that had the same balance as the randomized group.

The Bonferroni correction was applied to adjust the significance threshold for the ITT analysis of the 11 secondary outcomes. Nominal *P* values less than .05/11 = .005 were regarded as statistically significant for the ITT analysis of the secondary efficacy outcomes as per the Bonferroni correction. Descriptive statistics were used for study variables (including age, sex, and months in the study) with frequency tabulations for categorical variables and summary statistics (mean and range) for continuously distributed variables. Safety was assessed in participants completing the study using descriptive statistics. Statistical analysis was performed using R (R Foundation), version 3.2.1. The parallel line plot was created using SAS (SAS Institute), version 9.4.

Early Termination Criteria

Two interim analyses for demonstration of efficacy were planned (after the primary outcome had been ascertained for one-third and two-thirds of the 100 targeted evaluable participants), using an O'Brien-Fleming boundary to preserve studywise type I error of 2.5% (1-sided). The nominal *P* values for significance at the 2 interim and final analyses were less than .001, .007, and .02, respectively. There was no formal early stopping criterion based on futility.

Results

Demographic Characteristics of Participants

From July 2010 through June 2014, 156 participants were assessed for eligibility (Figure 1). Sixty-four participants were excluded, as they did not meet the inclusion criteria or declined to participate. Ninety-two participants were randomized after the baseline endoscopy. The data and safety monitoring board (DSMB) reviewed the study at the first interim analysis of 33 participants. Although the prespecified interim stopping rule had been met the at that point, the DSMB recommended continuation of the study. Study investigators were not made aware of the results of the interim analysis. The study was stopped after the second interim analysis of 67 participants by the DSMB because the prespecified stopping rule for the primary end point was met. All participants and investigators remained blinded to randomization status until the final study participant completed their end point endoscopy. At the time of the DSMB decision to stop the study, 92 participants had been randomized and were included in the intention-to-treat analysis: 46 participants in the sulindac-erlotinib group and 46 in the placebo group. Fourteen participants withdrew before the end point endoscopy examination and 5 participants did not receive end point examinations due to the early halt of the study; thus, 73 randomized participants completed the study with pretreatment and posttreatment endoscopy results and were included in the per-protocol analysis: 37 participants received sulindac-erlotinib and 36 placebo (Figure 1).

Demographic characteristics between the treatment and placebo groups, including age, were similar (**Table 1**). Overall, 61% of participants were women, with sexes equitably distributed between the treatment and placebo groups. Participants with classic and attenuated FAP were randomized to the treatment groups separately, yielding similar distributions (30% attenuated FAP and 70% classic FAP) in each group. A germline *APC* mutation was confirmed in 88% of participants, including all participants with attenuated FAP.

Outcomes

Primary Outcome

The change in total duodenal polyp burden, defined as the change in the median sum diameter of polyps, was significantly different between the placebo and sulindac-erlotinib groups at 6 months. There was an 8-mm median increase from baseline in the placebo group and an 8.5-mm median decrease from baseline in the sulindac-erlotinib group (between-group difference, −19.0 mm [95% CI, −32.0 to −10.9], $P < .001$) (**Figure 2** and **Table 2**). This is also presented as a percentage of change in duodenal polyp burden in Table 2, showing a 30.6% increase from baseline in the placebo group and a 37.9% decrease from baseline in the sulindac-erlotinib group (between-group difference, −71.2% [95% CI, −100.2% to −45.3%], $P < .001$).

Secondary Outcomes

In a subgroup analysis of participants with classic FAP (n = 64) or attenuated FAP (n = 28), the differences in duodenal polyp burden with treatment vs placebo were still significant for both results (between-group difference for treatment vs placebo: for participants with classic FAP, −20.0 mm [95% CI, −37.0 to 9.7], $P < .001$; for participants with attenuated FAP, −18.0 mm [95% CI, −33.0 to −8.8], $P < .001$) (Table 2).

Table 1. Baseline Demographic Characteristics of Participants (N = 92)

Characteristic	Sulindac-Erlotinib Group (n = 46)	Placebo Group (n = 46)
Age, mean (SD), y	42 (14)	41 (14)
Sex, No. (%)		
Men	18 (39)	18 (39)
Women	28 (61)	28 (61)
Height, mean (SD), cm	169 (11)	169 (10)
Weight, mean (SD), kg	83 (23)	86 (26)
BMI, mean (SD)	28.1 (7.2)	30.1 (8.4)
Smoking, No. (%)	3 (7)	9 (20)
Alcohol consumption, No. (%)	17 (37)	17 (37)
Eligibility status, No. (%)[a]		
Clinical diagnosis	7 (15)	4 (9)
Genetic diagnosis	39 (85)	42 (91)
FAP status, No. (%)		
Classic[b]	32 (70)	32 (70)
Clinical diagnosis	7	4
Genetic diagnosis	25	28
Attenuated[c]	14 (30)	14 (30)
Clinical diagnosis	0	0
Genetic diagnosis	14	14
Colon status, No. (%)		
Intact colon	11 (24)	10 (22)
Ileal-pouch anal anastomosis	21 (46)	23 (50)
Ileorectal anastomosis	9 (20)	9 (20)
Ileostomy	5 (11)	4 (9)
No. of polyps, median (IQR)	13.5 (8.0-28.5)	10.5 (7.0-26.8)
Sum of diameter of polyps, median (IQR), mm	29.0 (13.5-60.8)	23.0 (12.0-52.5)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FAP, familial adenomatous polyposis; IQR, interquartile range.

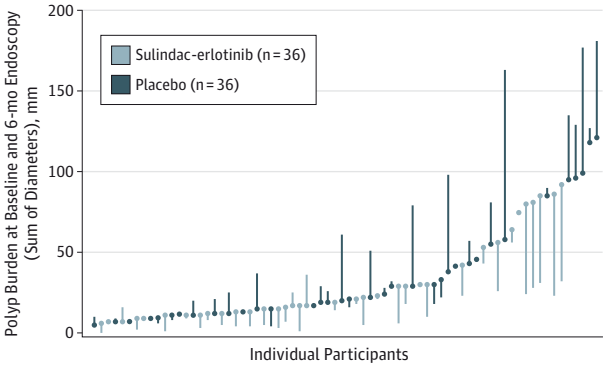
[a] Genetic diagnosis was defined as identification of a pathologic mutation of the adenomatous polyposis coli (*APC*) gene. Clinical diagnosis was defined as phenotype consistent with classic FAP.

[b] Classic FAP was defined as presentation with greater than 100 colonic adenomas and either (1) multiple family members with a classic FAP phenotype or (2) an *APC* mutation in a region of the gene known to correlate with classic FAP, or (3) both.

[c] Attenuated FAP was defined as presence of a mutation in a portion of the *APC* gene known to correlate with attenuated FAP and presentation of a milder phenotype in terms polyp density in the participant and the family. All participants with attenuated FAP in this study had a confirmed mutation in the *APC* gene.

Both a per-protocol analysis (n = 73) and a subgroup analysis limited to the 81 participants with a confirmed germline *APC* mutation (genetic diagnosis subgroup analysis) showed consistent results. In both analyses, treatment was associated with a significant reduction in duodenal polyp burden compared with placebo (between-group difference for treatment vs placebo: for per-protocol analysis, −19.5 mm [95% CI, −33.0 to −11.0], $P < .001$; for germline *APC* mutation subgroup analysis, −19.2 mm [95% CI, −30.8 to −11.7, $P < .001$) (Table 2).

Figure 2. Per-Protocol Analysis of Change in Total Sum of Diameters of Duodenal Polyps for Each Participant Taking Sulindac-Erlotinib vs Those Taking Placebo



Each participant is represented by a vertical bar starting at their baseline polyp burden and running to the 6-month polyp burden. The length of the vertical bar portrays the magnitude of change. The participants are ordered by baseline polyp burden. One participant not included in this Figure was described as "carpeted" with small polyps throughout the duodenum. Polyp burden at baseline was estimated as 700 mm. Endoscopy at the 6-month time point indicated no change for this participant. Circles indicate baseline data; data for some individuals were unchanged at 6 months (circles alone).

For total duodenal polyp count, the median increase was 4.3 polyps in the placebo group, but decreased by 2.8 polyps in the sulindac-erlotinib group (between-group difference, −8.0 polyps [95% CI, −12.2 to −4.7], $P < .001$) (**Table 3**). Subgroup analyses confirmed similar findings in participants with classic or attenuated FAP and a genetic diagnosis.

The chemopreventive effect was evaluated across participants with a wide range of polyp numbers at baseline endoscopy. The median total duodenal polyp burden decreased by 6.5 mm (between-group difference, −9.1 mm [95% CI, −15.5 to −3.8], $P < .001$) compared with baseline among participants with a low initial polyp burden (sum of diameters, ≤21 mm). For participants with a high initial duodenal polyp burden (sum of diameters, >21 mm) the treatment effect size was much larger, with a median decrease of 13.3 mm in polyp burden (between-group difference, −36.6 mm [95% CI, −57.8 to −19.5], $P < .001$) compared with baseline (Table 2). An endoscopic view of duodenal polyposis before and after 6 months of treatment with sulindac and erlotinib is shown in eFigure 1 in Supplement 2.

To assess the activation status of EGFR in the polyps, we determined the level of phosphorylated EGFR in polyp lysates and found detectable phosphorylated EGFR in 6 of 7 polyps from the placebo group (eFigure 2 in Supplement 2; placebo group shown in lanes 8-14, with phosphorylated EGFR detectable in lanes 9-14), but minimal or no phosphorylated EGFR in 7 of 7 polyps harvested from the sulindac-erlotinib-treated group (eFigure 2 in Supplement 2; in lanes 1-7). These data indicate that the sulindac-erlotinib treatment effectively limited activation of EGFR.

Table 2. Change in Sum Diameter of Duodenal Polyp Burden From Baseline for Intention-to-Treat, Genetic Diagnosis Subgroup, and Per-Protocol Analyses

	Duodenal Polyp Burden (Sum of Diameters), mm							
				Change (6-mo Follow-up − Baseline), Median (IQR)[a,b]		Net Between-Group Differences (95% CI)[b,c]		
	No. of Participants	Baseline, Median (IQR)	6-mo Follow-up, Median (IQR)	Median Change	Median Change, %		*P* Value	Net % Change[b,c]
Intention-to-Treat Analysis (N = 92)								
Sulindac-erlotinib	46	29.0 (13.5 to 60.8)	19.5 (17.0 to 23.0)	−8.5 (−9.5 to −7.0)	−37.9 (−51.0 to −27.3)	−19.0 (−32.0 to −10.9)	<.001	−71.2 (−100.2 to −45.3)
Placebo	46	23.0 (12.0 to 52.5)	31.0 (27.0 to 37.3)	8.0 (5.0 to 9.5)	30.6 (17.5 to 36.8)			
Classic FAP[d]								
Sulindac-erlotinib	32	46.0 (16.8 to 73.2)	27.5 (24.5 to 30.0)	−8.5 (−9.5 to −7.3)		−20.0 (−37.0 to −9.7)	<.001	
Placebo	32	29.5 (16.5 to 55.5)	42.0 (31.3 to 49.1)	8.5 (4.5 to 11.3)				
Attenuated FAP[e]								
Sulindac-erlotinib	14	15.0 (9.5 to 21.2)	7.0 (6.0 to 8.5)	−8.0 (−9.5 to −5.5)		−18.0 (−33.0 to −8.8)	<.001	
Placebo	14	13.0 (11.0 to 26.5)	24.5 (18.5 to 29.0)	7.0 (5.0 to 9.5)				
Polyp burden								
High[f]								
Sulindac-erlotinib	26	56.5 (32.8 to 80.8)	30.0 (28.0 to 33.5)	−13.3 (−18.0 to −9.6)		−36.6 (−57.8 to −19.5)	<.001	
Placebo	24	50.0 (31.5 to 87.5)	80.0 (66.3 to 89.2)	14.2 (9.0 to 24.1)				
Low[g]								
Sulindac-erlotinib	20	12.5 (10.5 to 16.2)	5.5 (5.0 to 7.0)	−6.5 (−7.0 to −5.0)		−9.1 (−15.5 to −3.8)	<.001	
Placebo	22	11.5 (9.2 to 16.5)	15.9 (12.3 to 18.0)	3.0 (1.0 to 6.0)				
Genetic Diagnosis Subgroup Analysis (n = 81)[h]								
Sulindac-erlotinib	39	21.0 (12.5 to 54.5)	14.0 (9.7 to 18.0)	−9.0 (−9.0 to − 8.0)		−19.2 (−30.8 to −11.7)	<.001	
Placebo	42	23.0 (11.2 to 56.5)	32.5 (28.0 to 42.0)	9.0 (6.0 to 11.1)				
Per-Protocol Analysis (n = 73)								
Sulindac-erlotinib	37	19.0 (12.0 to 53.0)	14.0 (5.0 to 26.0)	−9.0 (−17.0 to −2.0)	−56.3 (−70.0 to −14.3)	−19.5 (−33.0 to −11.0)	<.001	−75.5 (−100.4 to −52.9)
Placebo	36	22.0 (12.0 to 44.0)	28.0 (15.0 to 80.0)	6.0 (0.0 to 27.0)	30.6 (0.0 to 79.6)			

Abbreviations: FAP, familial adenomatous polyposis; IQR, interquartile range.

[a] Change is calculated individually for each participant (6-month polyp burden minus baseline polyp burden and the associated percentage of change). The median change within treatment and placebo groups represents the 50th percentile of these calculated changes.

[b] The median of the differences does not necessarily equal the difference between the medians.

[c] Hodges-Lehmann estimates of net difference and the associated percentage of change reflect the difference in the group change from 6 months to baseline. These estimates were calculated for each sample. Percentile bootstrap confidence intervals were calculated for the Hodges-Lehmann estimator.

[d] Classic FAP was defined as presentation with more than 100 colonic adenomas and either (1) multiple family members with a classic FAP phenotype or (2) an adenomatous polyposis coli (*APC*) mutation in a region of the gene known to correlate with classic FAP, or (3) both.

[e] Attenuated FAP was defined as the presence of a mutation in a portion of the *APC* gene known to correlate with attenuated FAP and presentation of a milder phenotype in terms polyp density in the participant and the family. All participants with attenuated FAP had a confirmed mutation in the *APC* gene.

[f] High polyp burden was defined as baseline total sum of diameters is greater than the median of 21 mm.

[g] Low polyp burden was defined as baseline total sum of diameters is less than or equal to the median of 21 mm.

[h] Genetic diagnosis was defined as participants identified with a pathologic mutation of the *APC* gene. Data presented are that for polyp burden.

Study Safety

Treatment with sulindac-erlotinib for a 6-month period was generally well tolerated. Adverse events were reported in 76 individuals (83%), with 27 of the total 92 enrolled participants (29%) having grade 2 or 3 adverse events (**Table 4**). No grade 4 events were reported. The most common adverse event was an erlotinib-induced acneiform-like rash, which occurred in 87% of the treatment group (n = 40) and 20% of the placebo group (n = 9) ($P < .001$). The rash was managed with topical cortisone and/or clindamycin therapy. Additional adverse events commonly increased in the treatment group included oral mucositis (39.1%; n = 18), diarrhea (26%; n = 12), and nausea (23.9%; n = 11). More individuals in the treatment group (46%; n = 21) vs placebo group

Table 3. Change in Number of Duodenal Polyps From Baseline in the Intention-to-Treat Analysis

	No. of Participants	No. of Duodenal Polyps				
		Baseline, Median (IQR)	6-mo Follow-up, Median (IQR)	Change (6-mo Follow-up − Baseline), Median (IQR)[a,b]	Net Between-Group Difference (95% CI)[b,c]	*P* Value
All participants						
Sulindac-erlotinib	46	13.5 (8.0 to 28.5)	10.0 (9.0 to 11.0)	−2.8 (−4.0 to −1.5)	−8.0 (−12.2 to −4.7)	<.001
Placebo	46	10.5 (7.0 to 26.8)	17.0 (13.1 to 20.0)	4.3 (3.1 to 5.5)		
Classic FAP[d]						
Sulindac-erlotinib	32	19.0 (9.5 to 32.2)	14.5 (12.5 to 17.0)	−2.1 (−4.0 to −0.5)	−7.1 (−13.2 to −3.0)	<.001
Placebo	32	16.0 (7.8 to 32.2)	20.5 (16.7 to 27.9)	4.0 (2.5 to 5.6)		
Attenuated FAP[e]						
Sulindac-erlotinib	14	7.5 (4.2 to 11.0)	4.0 (4.0 to 4.0)	−4.3 (−6.0 to −2.5)	−9.7 (−15.2 to −5.4)	<.001
Placebo	14	6.5 (5.2 to 13.0)	11.0 (9.0 to 13.0)	4.9 (3.6 to 6.0)		
Genetic Diagnosis[f]						
Sulindac-erlotinib	39	11.0 (7.0 to 20.0)	8.0 (6.0 to 10.0)	−3 (−4.8 to −2.0)	−9 (−13.1 to −5.7)	<.001
Placebo	42	10.0 (6.2 to 30.8)	17.2 (14.5 to 20.0)	5.0 (4.0 to 6.0)		

Abbreviations: FAP, familial adenomatous polyposis; IQR, interquartile range.

[a] Change is calculated individually for each participant (6-month polyp burden minus baseline polyp burden). The median change within treatment and placebo groups represents the 50th percentile of these calculated changes.

[b] The median of the differences does not necessarily equal the difference between the medians.

[c] Hodges-Lehmann estimates of net difference reflect the difference in the group change from 6 months to baseline. These estimates were calculated for each sample. Percentile bootstrap confidence intervals were calculated for the Hodges-Lehmann estimator.

[d] Classic FAP was defined as presentation with more than 100 colonic adenomas and either (1) multiple family members with a classic FAP phenotype or (2) an adenomatous polyposis coli (*APC*) mutation in a region of the gene known to correlate with classic FAP, or (3) both.

[e] Attenuated FAP was defined as presence of a mutation in a portion of the *APC* gene known to correlate with attenuated FAP and presentation of a milder phenotype in terms polyp density in the participant and the family. All participants with attenuated FAP had a confirmed mutation in the *APC* gene.

[f] Genetic diagnosis was defined as identification of a pathologic mutation of the *APC* gene.

Table 4. Incidence and Severity of Adverse Events for Total Participants With FAP (N=92) Taking Sulindac-Erlotinib vs Placebo[a]

	Toxicity, No. of Events (%)[c]						
	Sulindac-Erlotinib Group (n = 46)			Placebo Group (n = 46)			
Grade Terminology[b]	None	Grade 1	Grade 2 or 3	None	Grade 1	Grade 2 or 3	*P* Value Fisher Exact Test
Total individuals, highest grade	3 (6.5)	22 (47.8)	21 (45.7)[d]	13 (28.3)	27 (58.7)	6 (13.0)[d]	<.001
Rash acneiform	6 (13.0)	28 (60.9)	12 (26.1)	37 (80.4)	9 (19.6)	0	<.001
Oral mucositis	28 (60.9)	15 (32.6)	3 (6.5)[d]	41 (89.1)	5 (10.9)	0	.004
Diarrhea	34 (73.9)	10 (21.7)	2 (4.3)	40 (87.0)	6 (13.0)	0	.16
Nausea	35 (76.1)	11 (23.9)	0	40 (87.0)	4 (8.7)	2 (4.3)	.06
Pain in extremity	42 (91.3)	4 (8.7)	0	36 (78.3)	8 (17.4)	2 (4.3)	.17
Dry skin	39 (84.8)	7 (15.2)	0	39 (84.8)	7 (15.2)	0 (0)	>.99
Abdominal pain	42 (91.3)	4 (8.7)	0	38 (82.6)	6 (13.0)	2 (4.3)[d]	.30
Dry eye (irritation)	37 (80.4)	9 (19.6)	0	45 (97.8)	1 (2.2)	0	.02
Headache	42 (91.3)	4 (8.7)	0	38 (82.6)	5 (10.9)	3 (6.5)	.30
Fatigue	41 (89.1)	5 (10.9)	0	41 (89.1)	5 (10.9)	0	>.99
Alopecia	41 (89.1)	5 (10.9)	0	45 (97.8)	1 (2.2)	0	.20
Dyspepsia	42 (91.3)	3 (6.5)	1 (2.2)	44 (95.7)	2 (4.3)	0	.70
AST and/or ALT increase	43 (93.5)	2 (4.3)	1 (2.2)	42 (91.3)	4 (8.7)	0	.70
Hypertension	43 (93.5)	1 (2.2)	2 (4.3)	46 (100)	0	0	.24
Hematochezia	43 (93.5)	1 (2.2)	2 (4.3)	46 (100)	0	0	.24
Blurred vision	45 (97.8)	0	1 (2.2)	46 (100)	0	0	>.99

Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; FAP, familial adenomatous polyposis.

[a] Observed in 5% or more of patients or grade 2 or higher toxicity and possibly related to study drug. Presented as number of individuals.

[b] Grade terminology was from the Common Terminology Criteria for Adverse Events from the US Department of Health and Human Services, version 4.

[c] Participants could have more than 1 type of event.

[d] One case with a grade 3 adverse event.

(13%; n = 6) experienced grade 2 or 3 adverse events. Nineteen participants (10 taking placebo and 9 taking treatment) withdrew from the study; 5 due to early study halt, 5 due to drug-induced adverse effects or possible allergic reaction, 3 due to unrelated health reasons, 3 were lost to follow-up, 1 was noncompliant, and 2 for pregnancy beginning during study course (both of whom were taking placebo).

Of those who completed the study, 28% of participants taking placebo and 73% of participants taking treatment had erlotinib-dose reduction. Twenty-eight percent of patients taking placebo and 54% of patients taking treatment had sulindac-dose reduction at some point during the study. Erlotinib-dose reductions included 16 cases of grade 1 and 2 rash, which were found to be intolerable by the participant. In addition, there were 11 patients for whom study drugs were temporarily discontinued due to concern for gastrointestinal bleeding (n = 6), elevated alanine aminotransferase level (n = 1), elevated blood pressure (n = 1), ocular pain or change in vision (n = 2), and tonsillitis (n = 1). Three participants had their erlotinib dose reduced to 50 mg per day, 13 participants had a reduction to 25 mg per day, and 11 participants had a temporary discontinuation of both study drugs. When symptoms improved, erlotinib and sulindac were reescalated as tolerated. Only 4 participants had their erlotinib dose fully reescalated to 75 mg per day, 7 participants ended at 50 mg per day, 16 participants ended at 25 mg per day. The median administered dose of sulindac was 287.4 mg/d (range, 131.7-300.0) and erlotinib was 48.7 mg/d (range, 23.3-75.0). There was no correlation between total drug consumed and response, indicating that the study was conducted within the range of efficacy, even when participants reduced their dose.

Discussion

In this double-blind, placebo-controlled, randomized trial, sulindac in combination with erlotinib effectively reduced the total duodenal polyp burden and polyp number in participants with FAP compared with placebo. This effect was significant after 6 months of therapy and was observed in both classic and attenuated FAP participants.

Several investigators have described regression of colorectal adenomatous polyps in patients with FAP who received sulindac alone; however, sulindac has not been effective in reducing duodenal polyposis.[5,6]

Preclinical data suggested a beneficial role for EGFR inhibition in FAP. These studies showed a greater than 85% decrease in the progression of intestinal microadenomas through genetic or biochemical inhibition of EGFR tyrosine kinase activity in the *Apc*$^{Min/+}$ mouse model of FAP.[15,16] *Apc*$^{Min/+}$ mice form predominantly small intestinal adenomas, suggesting potential efficacy of EGFR inhibition in the duodenum. EGFR inhibitors are successfully used in the current treatment of non-small cell lung cancer lacking oncogenic *KRAS* mutation.[17-19] Although *KRAS* mutations are frequent in colorectal tumors, they are infrequent in aberrant crypt foci in patients with FAP,[17-19] suggesting that EGFR inhibitors might be more active in early vs late intestinal neoplasms in patients with FAP. Our trial suggests the effects of COX and EGFR inhibition observed in the murine models may be observed in the small intestine of patients with FAP as well.

Mortality from colorectal cancer in FAP has been markedly reduced by colorectal surveillance with colonoscopy and prophylactic colectomy, whereas the increased risk of duodenal adenocarcinoma remains.[20-22] For patients with advanced neoplasia of the duodenum, surgical therapy has been the standard of care. However, duodenectomy and Whipple procedure are associated with significant morbidity and mortality, and surgical or endoscopic polypectomy results in a high rate of recurrent polyps.[23,24] Our study suggests the possibility of an effective chemoprevention strategy for duodenal neoplasia in patients with FAP and supports the need for future longer-term studies to establish clinically meaningful outcomes.

There was a high rate of grade 1 and grade 2 adverse events in our study, the most notable were an acneiform rash in 87% of participants and oral mucositis in 39% of participants in the treatment group. Although the dosing of sulindac was based on prior chemoprevention studies,[5,6] the dosing of erlotinib was estimated from cancer treatment and lung cancer chemotherapy trials.[25,26] Dose-ranging studies will be needed to determine if lower and/or less-frequent dosing of erlotinib could diminish these adverse effects, but retain efficacy. Though all participants started the trial taking fixed standard doses of the 2 study medications, dose modifications due to intolerance led to a range of doses. We found equal efficacy in causing polyp regression across the resulting range of erlotinib doses used. The incomplete efficacy of sulindac and erlotinib in some participants necessitates continued endoscopic surveillance and surgery for advanced duodenal neoplasia at the dosing levels and duration of our study.

Limitations to this study should be noted. First, because the study measured polyp regression, it is unknown if sulindac and erlotinib would be effective in preventing the emergence of new duodenal adenomas. This issue arose in a pediatric FAP trial that suggested sulindac may be ineffective in preventing the emergence of colonic adenomas in children with FAP.[27] Second, without long-term follow-up data, the durability of the effect of sulindac and erlotinib, the potential to develop resistance to either drug, and whether patients ultimately undergo fewer surveillance endoscopies/surgery or develop fewer cancers are unknown. Studies in *Apc*$^{min/+}$ mice have suggested long-term use of sulindac resulted in an eventual loss of efficacy[28,29] and breakthrough cancers in humans have been reported, raising concern about its ability to reduce malignant transformation.[30,31] Third, both sulindac and erlotinib can be associated with rare and serious adverse effects such as cardiotoxicity[32] and interstitial lung disease,[33,34] respectively, though no such effects were encountered in our study. Fourth, our study did not randomize according to Spigelman classification, because polyps were not removed for histologic analysis unless it was medically indicated;

however, the preventive effect was seen in participants stratified by high or low duodenal polyp burdens. Fifth, this cohort was not sufficient in size to study the effects of erlotinib or sulindac alone, and the potential of synergistic activity led to the testing of the combination instead. Sixth, studies that are terminated early for efficacy may overestimate the true effect size. These issues emphasize the need for further research, including more definitive clinical chemoprevention trials in FAP to investigate resistance, long-term, clinically meaningful end points, dose-ranging, and need for continuous or cyclic therapy.

Conclusions

Among participants with FAP, the use of sulindac and erlotinib compared with placebo resulted in a lower duodenal polyp burden after 6 months. However, the frequency of adverse events may limit the use of these medications at the doses used in this study. Further research is necessary to evaluate these preliminary findings in a larger study population with longer follow-up to determine whether the observed effects will result in improved clinical outcomes.

ARTICLE INFORMATION

Author Affiliations: Huntsman Cancer Institute, University of Utah, Salt Lake City (Samadder, Neklason, Boucher, Samowitz, Jones, Tavtigian, Done, Berry, Jasperson, Pappas, Smith, Sample, Davis, Topham, Burt); Department of Medicine (Gastroenterology), University of Utah, Salt Lake City (Samadder, Byrne, Kanth, Burt); Department of Oncological Sciences, University of Utah, Salt Lake City (Neklason, Jones, Tavtigian, Topham, Burt); Department of Medicine (Genetic Epidemiology), University of Utah, Salt Lake City (Neklason); Department of Medicine (Epidemiology), University of Utah, Salt Lake City (Boucher); Department of Pathology, University of Utah, Salt Lake City (Samowitz); Department of Medicine (Pulmonary), University of Utah, Salt Lake City (Topham); Department of Gastroenterology, University of Texas MD Anderson Cancer Center, Houston (Lynch); Penrose Hospital, Colorado Springs, Colorado (Strait); University of Vermont Cancer Center, Burlington (McKinnon); Department of Medicine, University of Hawaii, Honolulu (Kuwada).

Author Contributions: Drs Samadder and Neklason had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Samadder, Neklason, Boucher, Jones, Burt, Kuwada.
Acquisition, analysis, or interpretation of data: Samadder, Neklason, Byrne, Kanth, Samowitz, Boucher, Tavtigian, Done, Berry, Jasperson, Pappas, Smith, Sample, Davis, Topham, Lynch, Strait, McKinnon, Burt, Kuwada.
Drafting of the manuscript: Samadder, Neklason, Boucher, Pappas, Topham, Burt.
Critical revision of the manuscript for important intellectual content: Samadder, Neklason, Byrne, Kanth, Samowitz, Boucher, Jones, Tavtigian, Done, Berry, Jasperson, Smith, Sample, Davis, Lynch, Strait, McKinnon, Burt, Kuwada.
Statistical analysis: Boucher, Tavtigian, Pappas.
Obtained funding: Samadder, Jones, Tavtigian, Burt, Kuwada.
Administrative, technical, or material support: Samadder, Neklason, Byrne, Kanth, Done, Berry, Jasperson, Smith, Sample, Davis, Topham, Lynch, McKinnon, Burt, Kuwada.
Study supervision: Samadder, Neklason, Jones, Burt.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Samadder reports being a consultant for Cook Medical. Dr Jasperson reports being an employee of Ambry Genetics. Dr Burt reports being a consultant for Myriad Genetics and receiving personal fees from Thetis Pharmaceuticals. No other disclosures were reported.

Funding/Support: This project was funded by provided by grant P01-CA073992 from the National Cancer Institute (Drs Burt and Tavtigian); the Huntsman Cancer Institute Cancer Center Support Grant (NCI P30CA042014), as well as by the Huntsman Cancer Foundation; by a junior faculty career development award from the American College of Gastroenterology (Dr Samadder); and by grant 1ULTR001067 from the National Institutes of Health National Center for Advancing Translational Sciences.

Role of the Funder: The funders did not play a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Additional Contributions: We thank Tom Greene, PhD, John Fang, MD, John Valentine, MD, Curt Hagedorn, MD, Wendy Kohlmann, MS, Amanda Gammon, MS, Marjan Champine, MS, Deepika Nathan, MS, Mikaela Larson, BS, Lindsey Martineau, BS, Cristina Christenson, MPH, Megan Keener, BS, Angela Snow, MS (all at the University of Utah), for assisting with the clinical trial and patient care related to it. We also thank our external data safety monitoring board members for their assistance in the successful completion of this trial: Paul Limburg, MD (Mayo Clinic), David Weinberg, MD (Fox Chase Cancer Center), Sonia Kupfer, MD (University of Chicago), William Grady, MD (University of Washington), and Richard Holubkov, PhD (University of Utah). We thank Marc Greenblatt, MD (University of Vermont), for patient referrals into this study. We thank Ellen T. Wilson, PhD (University of Utah), for her help in editing the manuscript. Members of the external data and safety monitoring board were provided with a nominal honorarium and travel expense reimbursement for their participation in on-site safety and interim analysis meetings annually. All others received no compensation for their contributions.

REFERENCES

1. Groden J, Thliveris A, Samowitz W, et al. Identification and characterization of the familial adenomatous polyposis coli gene. *Cell*. 1991;66(3):589-600.

2. Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. *Gastroenterology*. 2010;138(6):2044-2058.

3. Biasco G, Pantaleo MA, Di Febo G, Calabrese C, Brandi G, Bülow S. Risk of duodenal cancer in patients with familial adenomatous polyposis. *Gut*. 2004;53(10):1547.

4. Conio M, Gostout CJ. Management of duodenal adenomas in 98 patients with familial adenomatous polyposis. *Gastrointest Endosc*. 2001;53(2):265-266.

5. Giardiello FM, Hamilton SR, Krush AJ, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med*. 1993;328(18):1313-1316.

6. Giardiello FM, Yang VW, Hylind LM, et al. Primary chemoprevention of familial adenomatous polyposis with sulindac. *N Engl J Med*. 2002;346(14):1054-1059.

7. Debinski HS, Trojan J, Nugent KP, Spigelman AD, Phillips RK. Effect of sulindac on small polyps in familial adenomatous polyposis. *Lancet*. 1995;345(8953):855-856.

8. Nugent KP, Farmer KC, Spigelman AD, Williams CB, Phillips RK. Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis. *Br J Surg*. 1993;80(12):1618-1619.

9. Phillips RK, Wallace MH, Lynch PM, et al; FAP Study Group. A randomised, double blind, placebo controlled study of celecoxib, a selective cyclooxygenase 2 inhibitor, on duodenal polyposis in familial adenomatous polyposis. *Gut*. 2002;50(6):857-860.

10. Arber N, Eagle CJ, Spicak J, et al; PreSAP Trial Investigators. Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med*. 2006;355(9):885-895.

11. Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med*. 2000;342(26):1946-1952.

12. Woodcock J. Withdrawal of approval of familial adenomatous polyposis indication for Celebrex. https://federalregister.gov/articles/2012/06/08/2012-13900/pfizer-inc-withdrawal-of-approval-of-familial-adenomatous-polyposis-indication-for-celebrex. Accessed February 29, 2016.

13. Coffey RJ, Hawkey CJ, Damstrup L, et al. Epidermal growth factor receptor activation induces nuclear targeting of cyclooxygenase-2, basolateral release of prostaglandins, and mitogenesis in polarizing colon cancer cells. *Proc Natl Acad Sci U S A*. 1997;94(2):657-662.

14. Eisinger AL, Nadauld LD, Shelton DN, et al. The adenomatous polyposis coli tumor suppressor gene regulates expression of cyclooxygenase-2 by a mechanism that involves retinoic acid. *J Biol Chem*. 2006;281(29):20474-20482.

15. Roberts RB, Min L, Washington MK, et al. Importance of epidermal growth factor receptor signaling in establishment of adenomas and maintenance of carcinomas during intestinal tumorigenesis. *Proc Natl Acad Sci U S A*. 2002;99(3):1521-1526.

16. Torrance CJ, Jackson PE, Montgomery E, et al. Combinatorial chemoprevention of intestinal neoplasia. *Nat Med*. 2000;6(9):1024-1028.

17. Marks JL, Broderick S, Zhou Q, et al. Prognostic and therapeutic implications of EGFR and KRAS mutations in resected lung adenocarcinoma. *J Thorac Oncol*. 2008;3(2):111-116.

18. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med*. 2005;2(3):e73.

19. Sos ML, Zander T, Thomas RK, Staratschek-Jox A, Claasen J, Wolf J. Expression of signaling mediators downstream of EGF-receptor predict sensitivity to small molecule inhibitors directed against the EGF-receptor pathway. *J Thorac Oncol*. 2008;3(2):170-173.

20. Gibbons DC, Sinha A, Phillips RK, Clark SK. Colorectal cancer: no longer the issue in familial adenomatous polyposis? *Fam Cancer*. 2011;10(1):11-20.

21. Bülow S. Results of national registration of familial adenomatous polyposis. *Gut*. 2003;52(5):742-746.

22. Morton DG, Macdonald F, Haydon J, et al. Screening practice for familial adenomatous polyposis: the potential for regional registers. *Br J Surg*. 1993;80(2):255-258.

23. Bülow S, Björk J, Christensen IJ, et al; DAF Study Group. Duodenal adenomatosis in familial adenomatous polyposis. *Gut*. 2004;53(3):381-386.

24. Heiskanen I, Kellokumpu I, Järvinen H. Management of duodenal adenomas in 98 patients with familial adenomatous polyposis. *Endoscopy*. 1999;31(6):412-416.

25. Lynch TJ, Fenton D, Hirsh V, et al. A randomized phase 2 study of erlotinib alone and in combination with bortezomib in previously treated, advanced non–small cell lung cancer. *J Thorac Oncol*. 2009;4(8):1002-1009.

26. Wheatley-Price P, Ding K, Seymour L, Clark GM, Shepherd FA. Erlotinib for advanced non–small cell lung cancer in the elderly: an analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. *J Clin Oncol*. 2008;26(14):2350-2357.

27. Lynch PM, Ayers GD, Hawk E, et al. The safety and efficacy of celecoxib in children with familial adenomatous polyposis. *Am J Gastroenterol*. 2010;105(6):1437-1443.

28. Tonelli F, Valanzano R, Messerini L, Ficari F. Long-term treatment with sulindac in familial adenomatous polyposis: is there an actual efficacy in prevention of rectal cancer? *J Surg Oncol*. 2000;74(1):15-20.

29. Cruz-Correa M, Hylind LM, Romans KE, Booker SV, Giardiello FM. Long-term treatment with sulindac in familial adenomatous polyposis: a prospective cohort study. *Gastroenterology*. 2002;122(3):641-645.

30. Niv Y, Fraser GM. Adenocarcinoma in the rectal segment in familial polyposis coli is not prevented by sulindac therapy. *Gastroenterology*. 1994;107(3):854-857.

31. Thorson AG, Lynch HT, Smyrk TC. Rectal cancer in FAP patient after sulindac. *Lancet*. 1994;343(8890):180.

32. Sulindac [package insert]. Corona, CA: Watson Laboratories; 2008. http://pi.actavis.com/data_stream.asp?product_group=1310&p=pi&language=E. Accessed February 29, 2016.

33. Qi WX, Sun YJ, Shen Z, Yao Y. Risk of interstitial lung disease associated with EGFR-TKIs in advanced non–small cell lung cancer: a meta-analysis of 24 phase 3 clinical trials. *J Chemother*. 2015;27(1):40-51.

34. Shi L, Tang J, Tong L, Liu Z. Risk of interstitial lung disease with gefitinib and erlotinib in advanced non–small cell lung cancer: a systematic review and meta-analysis of clinical trials. *Lung Cancer*. 2014;83(2):231-239.