Supplementary Online Content

Samadder NJ, Kuwanda SK, Boucher KM, et al. Association of Sulindac and Erlotinib vs Placebo With Colorectal Neoplasia in Familial Adenomatous Polyposis: Secondary Analysis of a Randomized Clinical Trial [published online February 8, 2018]. *JAMA Oncol*. doi:10.1001/jamaoncol.2017.5431

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Baseline Demographic Characteristics of Participants

Characteristic	Intact Colon		Ileal Pouch (IPAA)		Ileorectal	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
N	11	11	21	23	9	7
Sex % (n)						
Female	55% (6)	36% (4)	57% (12)	74% (17)	67% (6)	57% (4)

Male	45% (5)	64% (7)	43% (9)	26% (6)	33% (3)	43% (3)
Age Median IQR	 33 28-52	 37 33-45	 40 31-51	 38 28-52	 56 44-64	 36 32-49
Classification[a] % (n)						
Attenuated FAP	73% (8)	82% (9)	14% (3)	4% (1)	33% (3)	43% (3)
Classic FAP	27% (3)	18% (2)	86% (18)	96% (22)	67% (6)	57% (4)
BMI Mean (IQR)	 28 (24-32)	 28 (27-31)	 25 (22-31)	 29 (27-34)	 27 (26-33)	 24 (24-38)
Alcohol:						
Yes	36% (4)	45% (5)	33% (7)	39% (9)	44% (4)	14% (1)
Smoking:						
Yes	9% (1)	27% (3)	10% (2)	13% (3)	0% (0)	29% (2)
Study Completion:						
Yes	100% (11)	82% (9)	67% (14)	83% (19)	78% (7)	57% (4)
Baseline Polyp count Median (IQR)	 39 (19-81)	 16 (4-26)	 5 (2-17)	 6 (0-22)	 7 (4-15)	 3 (2-12)

[a]Classic FAP: presentation with more 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 both. Attenuated FAP: 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 patient and the family. All patients with attenuated FAP in this study had a confirmed mutation in the APC gene.

Supplemental Table 2: **Change in colorectal polyp number from baseline for Per Protocol analysis**

Per Protocol	Colorectal Polyp Number							
				Change (6-mo follow-up – Baseline), Median (IQR)				
	No. of Participants	Baseline Median (IQR)	6-mo follow-up, Median (IQR)	Median Change	Median Change, %	Net Between-Group Differences	P value	Net % Change
Intact Colon (Colorectal)								
Sulindac-Erlotinib	11	39 (19, 81)	2 (1, 5)	-27 (-80.5, -15.5)	-96 (-99.1, -79.2)	-28	0.0012	-89.3
Placebo	9	16 (4, 26)	9 (4, 22)	-2 (-3, -2)	-8.3 (-43.8, -16.7)			
IPAA								
Sulindac-Erlotinib	14	5 (2, 17)	0 (0, 1)	-3.0 (-8.8, -2.0)	-99.9 (-99.9, -59.3)	-5.5	0.0028	-98.9
Placebo	19	6 (0, 22)	8 (2, 50)	0 (-2.0, 4.0)	0 (-11.8, 145.0)			
Rectum (IRA)								
Sulindac-Erlotinib	7	7 (4, 15)	6 (1, 19)	-1.0 (-7.0, 15.0)	-60.0 (-85.7, 150)	5.5	0.648	-66.0

Placebo	4	3 (2, 12)	13 (5, 21)	6.0 (3.0, 10.0)	97.1 (60, 119)			

Supplemental Results:

A logistic regression model adjusted for the covariates in the linear regression model used for multiple imputation indicated that the only covariate significantly associated with the probability of being missing is weight. The fitted regression is not highly predictive of observed missingness, so we also report an extreme case analysis below (Supplemental Table 1). In this extreme case analysis the worst outcome, maximum increase in polyps (29 more than at baseline) is imputed in the treatment group. The greatest observed reduction in polyps was 286. Since none of the subjects with missing endpoints had 286 polyps to begin with, the extreme case is that all those in the placebo group had complete reduction in polyps with an end count of 0. The analysis that seems most sensitive to the imputation method is within the IPAA group. This is not surprising as this group had the majority of the missing values. There were 7 IPAA subjects missing endpoints in the treatment group and 4 IPAA subjects missing endpoints in the placebo group.

Supplemental Table 3: Extreme case sensitivity analysis

	Per-protocol		**ITT**		**Worst case (complete recovery)**	
	net between group differences	P value	net between group differences	P value	net between group differences	P value
Intact Colon	-28	0.0012	-27.5	0.0086	-25.5	0.006141
IPAA	-5.5	0.0028	-14.5	0.0034	-1.5	0.5692
Rectum	5.5	0.648	-13	0.2407	8.5	0.4514

Supplemental Table 4: **Observed adverse events in those with baseline colorectal polyp counts**

	Treatment (N =41)				Placebo (N =41)			
Events Possibly and Probably related to Drug	**N pts with events**	**% of randomized subjects**	**N events**	**Grade 1: Grade 2/3**	**N pts with events**	**% of randomized subjects**	**N events**	**Grade 1: Grade 2/3**
Rash acneiform	28	68.3%	36	30:6	9	22.0%	12	11:1
Intact Colon	7	63.6%	9	7:2	3	27.3%	4	4:0
IPAA	13	61.9%	19	17:2	5	21.7%	7	6:1
Ileorectal	8	88.9%	8	6:2	1	14.3%	1	1:0
Mucositis Oral	13	31.7%	15	12:3	4	9.8%	4	4:0
Intact Colon	3	27.3%	3	3:0	1	9.1%	1	1:0
IPAA	7	33.3%	9	6:3	2	8.7%	2	2:0
Ileorectal	3	33.3%	3	3:0	1	14.3%	1	1:0
Diarrhea	10	24.4%	10	7:3	4	9.8%	5	3:2
Intact Colon	4	36.4%	4	3:1	1	9.1%	1	1:0
IPAA	3	14.3%	3	3:0	2	8.7%	3	1:2
Ileorectal	3	33.3%	3	1:2	1	14.3%	1	1:0
Dry Skin	4	9.8%	4	4:0	5	12.2%	5	5:0
Intact Colon	3	27.3%	3	3:0	1	9.1%	1	1:0
IPAA	1	4.8%	1	1:0	4	17.4%	4	4:0
Ileorectal	0	0.0%	0	0:0	0	0.0%	0	0:0
Nausea	10	24.4%	12	11:1	3	7.3%	3	2:1
Intact Colon	3	27.3%	4	4:0	1	9.1%	1	1:0
IPAA	5	23.8%	6	6:0	1	4.3%	1	1:0
Ileorectal	2	22.2%	2	1:1	1	14.3%	1	0:1
Eye irritation	7	17.1%	7	7:0	1	2.4%	1	1:0
Intact Colon	3	27.3%	3	3:0	1	9.1%	1	1:0
IPAA	3	14.3%	3	3:0	0	0.0%	0	0:0
Ileorectal	1	11.1%	1	1:0	0	0.0%	0	0:0

Fatigue	5	12.2%	5	5:0	2	4.9%	2	2:0
Intact Colon	1	9.1%	1	1:0	1	9.1%	1	1:0
IPAA	2	9.5%	2	2:0	1	4.3%	1	1:0
Ileorectal	2	22.2%	2	2:0	0	0.0%	0	0:0
Headache	4	9.8%	4	4:0	6	14.6%	6	4:2
Intact Colon	1	9.1%	1	1:0	3	27.3%	3	3:0
IPAA	2	9.5%	2	2:0	1	4.3%	1	1:0
Ileorectal	1	11.1%	1	1:0	2	28.6%	2	0:2
Blood in stool	2	4.9%	3	1:2	0	0.0%	0	0:0
Intact Colon	0	0.0%	0	0:0	0	0.0%	0	0:0
IPAA	2	9.5%	3	1:2	0	0.0%	0	0:0
Ileorectal	0	0.0%	0	0:0	0	0.0%	0	0:0
Abdominal pain	2	4.9%	2	2:0	3	7.3%	3	3:0
Intact Colon	1	9.1%	1	1:0	2	18.2%	2	2:0
IPAA	1	4.8%	1	1:0	0	0.0%	0	0:0
Ileorectal	0	0.0%	0	0:0	1	14.3%	1	1:0
Pain in extremity	2	4.9%	2	2:0	7	17.1%	7	7:0
Intact Colon	1	9.1%	1	1:0	1	9.1%	1	1:0
IPAA	1	4.8%	1	1:0	4	17.4%	4	4:0
Ileorectal	0	0.0%	0	0:0	2	28.6%	2	2:0

Other: treatment group only (AST increase, Bruising, Chest Pain, Dehydration, Depression, Dry mouth, Dyspnea, Epistaxis, fever, Hair growth, Hypertension, Localized edema, Sore throat, Weight loss, hair growth)
*Alopecia in both

Other: placebo group only (Appetite increase, Dizziness, Hot flashes, lung infection)