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ORIGINAL CONTRIBUTION

Combination of Sulindac and Eflornithine Delays the Need for Lower Gastrointestinal Surgery in Patients With Familial Adenomatous Polyposis: Post Hoc Analysis of a Randomized Clinical Trial

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BACKGROUND: Colectomy and proctocolectomy are the initial standard of care for patients with familial adenomatous polyposis. Pharmacotherapy to prevent the progression of polyposis and surgeries in the lower GI tract would be beneficial to patients with this disease.

OBJECTIVE: This analysis aimed to evaluate the impact of eflornithine-sulindac combination versus monotherapy in delaying time to disease progression in the lower GI tract of patients with familial adenomatous polyposis.

DESIGN: This is a post hoc analysis of a randomized phase 3 trial.

SETTING: This study was conducted in 21 hospitals in 7 countries treating patients with familial adenomatous polyposis.

PATIENTS: Adults with familial adenomatous polyposis were randomly assigned 1:1:1 into 3 arms.

INTERVENTIONS: Patients received either eflornithine (750 mg), sulindac (150 mg), or both once daily for up to 48 months.

MAIN OUTCOME MEASURES: Efficacy was evaluated as the time from randomization to predefined primary disease progression end points.

Funding/Support: This study was sponsored by Cancer Prevention Pharmaceuticals, Inc: Kathryn Grenier (VP, Clinical Operations), Eva Underwood (Senior Clinical Research Associate), and Andy Hadlington (European Program Manager) of Cancer Prevention Pharmaceuticals, Inc, managed the study.

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RESULTS: A total of 158 patients were included in the study. Disease progression was observed in 2 of 54 (3.7%), 9 of 53 (17.0%), and 10 of 51 (19.6%) patients with at least partial lower GI tract in the combination, sulindac, and eflornithine arms, corresponding to risk reductions of 80% ($p = 0.02$) and 83% ($p = 0.01$) between combination and sulindac or eflornithine. When endoscopic excision of adenomas ≥10 mm in size was censored, the need for major surgery was observed in 0 of 54, 7 of 53 (13.2%), and 8 of 51 (15.7%) patients in the combination, sulindac, and eflornithine arms, corresponding to risk reductions approaching 100% between combination and sulindac ($p = 0.005$) or combination and eflornithine ($p = 0.003$).

LIMITATIONS: This was a post hoc analysis, the sample size was small, and there were fewer than expected events.

CONCLUSIONS: Eflornithine-sulindac combination therapy was superior to either drug alone in delaying or preventing the need for lower GI tract surgery in patients with familial adenomatous polyposis. See **Video Abstract** at http://links.lww.com/DCR/B658.

***REGISTRATION*:** ClinicalTrials.gov, NCT01483144; EU Clinical Trials Register, EudraCT 2012-000427-41

LA COMBINACIÓN DE SULINDAC Y EFLORNITINA RETRASA LA NECESIDAD DE CIRUGÍA DEL TUBO DIGESTIVO BAJO EN PACIENTES CON PAF: ANÁLISIS POST-HOC DE UN ENSAYO CLÍNICO ALEATORIZADO

ANTECEDENTES: La colectomía y la proctocolectomía son el estándar inicial de atención para los pacientes con poliposis adenomatosa familiar. La farmacoterapia para prevenir la progresión de la poliposis y las cirugías en el tracto gastrointestinal inferior sería beneficiosa para los pacientes con esta enfermedad.

OBJETIVO: Este análisis tuvo como objetivo evaluar el impacto de la combinación de eflornitina-sulindac versus la monoterapia en el retraso del tiempo hasta la progresión de la enfermedad en el tracto gastrointestinal inferior de pacientes con poliposis adenomatosa familiar.

DISEÑO: Este es un análisis posthoc de un ensayo de fase 3 aleatorizado.

ENTORNO CLINICO: Veintiún hospitales en 7 países que tratan a pacientes con poliposis adenomatosa familiar.

PACIENTES: Adultos con poliposis adenomatosa familiar fueron aleatorizados 1: 1: 1 en 3 brazos.

INTERVENCIONES: Los pacientes recibieron eflornitina (750 mg), sulindac (150 mg) o ambos una vez al día durante un máximo de 48 meses.

PRINCIPALES MEDIDAS DE VALORACION: La eficacia se evaluó como el tiempo desde la aleatorización hasta los criterios de valoración primarios predefinidos de progresión de la enfermedad.

RESULTADOS: Los resultados se informan para la población de estudio excluyendo a los pacientes que se habían sometido a ileostomías permanentes ($n = 158$). Se observó progresión de la enfermedad en 2/54 (3,7%), 9/53 (17,0%) y 10/51 (19,6%) pacientes con al menos tracto gastrointestinal inferior parcial en los brazos de combinación, sulindac y eflornitina, respectivamente, correspondientes al riesgo de reducciones del 80% ($p = 0,02$) y del 83% ($p = 0,01$) entre la combinación y el sulindaco o la eflornitina, respectivamente. Cuando se censuró la escisión endoscópica de adenomas ≥10 mm de tamaño, se observó la necesidad de cirugía mayor en 0/54, 7/53 (13,2%) y 8/51 (15,7%) pacientes en la combinación, sulindac y eflornitina, respectivamente, correspondientes a reducciones de riesgo cercanas al 100% entre combinación y sulindac ($p = 0,005$) o combinación y eflornitina ($p = 0,003$).

LIMITACIONES: Este fue un análisis posthoc, el tamaño de la muestra fue pequeño y hubo menos eventos de los esperados.

Financial Disclaimers (*continued from page 536*): Prevention Pharmaceuticals, Ferring, and Janssen, and consultation fees from Freenome and SLA Pharma. Dr Dekker has received endoscopic equipment on loan and research grant from FujiFilm; consultation fees from Cancer Prevention Pharmaceuticals, FujiFilm, GI Supply, Olympus, and Tillots; and speaker fees from GI Supply, Olympus, and Roche. Dr Lynch has received research support from Cancer Prevention Pharmaceuticals and consultant fees from SLA Pharma. Dr Samadder has received consultant fees from Cancer Prevention Pharmaceuticals and Jannsen R&D. Dr Van Cutsem has been on advisory boards for Array, AstraZeneca, Bayer, Biocartis, Bristol-Myers Squibb, Celgene, Daiichi, GSK, Halozyme, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Pierre Fabre, Roche, Servier, Sirtex, and Taiho, and received research grants from Amgen, Bayer, Boehringer Ingelheim, Celgene, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, and Servier, all of which are paid to his institution. Dr Hüneburg has received consultation fees from Cancer Prevention Pharmaceuticals. Dr Du has received consultation fees from Cancer Prevention Pharmaceuticals. Drs Boytim, Bruckheimer, and Cohen are employees of Cancer Prevention Pharmaceuticals and own stock in the company. Drs Stoffel, Wise, Lim, and Church have nothing to declare.

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CONCLUSIONES: La terapia de combinación de eflornitina-sulindac fue superior a cualquier fármaco solo para retrasar o prevenir la necesidad de cirugía del tracto gastrointestinal inferior en pacientes con poliposis adenomatosa familiar. Consulte **Video Resumen** en http://links.lww.com/DCR/B658. *(Traducción—Dr. Adrian Ortega)*

KEY WORDS: Adenomatous polyposis coli; Eflornithine; Lower gastrointestinal tract; Sulindac; Treatment outcomes.

Familial adenomatous polyposis (FAP) is most commonly caused by germline mutations in the adenomatous polyposis coli (*APC*) gene and characterized initially by progressive development of hundreds to thousands of adenomatous polyps in the colon and rectum.[1–3] Regular colonoscopy surveillance is recommended from diagnosis until either colectomy with ileorectal anastomosis (IRA) or proctocolectomy with ileostomy or IPAA is indicated for prophylactic treatment of progressive polyposis, advanced disease, inability to adequately survey the colon to prevent cancer, or cancer.[4–6] In addition to the spectrum of potential complications associated with surgery, neither IRA nor IPAA are a cure for FAP.[6–10] Furthermore, they do not eliminate the need for continued surveillance[6–10] or additional surgery.[10–13] The surgical procedures negatively affect patients' quality of life (QoL).[10,12] Pharmacotherapy would enhance FAP disease management by delaying or avoiding the occurrence of advanced colorectal adenomas, the need for complex polypectomy, and/or the need for life-altering lower gastrointestinal (LGI) surgery.

Sulindac, a nonsteroidal anti-inflammatory drug that influences polyamine and cyclooxygenase metabolism,[14] has been used off-label for treatment of FAP with variable short-term success.[15–17] In a placebo-controlled study, treatment of patients with sporadic colorectal adenomas with a combination of sulindac and eflornithine reduced mucosal polyamines in the LGI tract and reduced the risk of metachronous advanced adenoma at 3 years.[18] In patients with FAP, a combination of eflornithine with celecoxib demonstrated a 40% reduction in global polyp burden.[19] In several other studies, treatment with sulindac alone delayed polyposis in the LGI tract among patients with FAP.[20] Thus, it is reasonable to expect that the primary effect of combination therapy with sulindac and eflornithine would be observed among patients with at least a partially intact LGI tract.

The CPP FAP-310 trial (NCT01483144), which compared the efficacy and safety of combination therapy with sulindac and eflornithine versus monotherapies, showed no statistical difference between the treatment arms using a composite primary end point that included prevention of both upper and lower GI surgery for up to 4 years.[21,22] Based on the available evidence, including the efficacy of this combination in preventing sporadic adenomas in the colorectum,[18] this combination therapy could be beneficial to patients who had FAP with an intact colon, retained rectum, or ileal pouch (LGI subpopulation). In this article, we report our post hoc analysis undertaken to evaluate the efficacy of combination therapy versus monotherapies focusing on delays in the need for life-altering LGI surgery due to adenoma progression in the LGI subpopulation.

MATERIALS AND METHODS

Study Design, Setting, and Participants

Details of the study design of this multinational, multicenter, double-blind, randomized trial, approved by all local institutional review boards, conducted at 21 centers in 7 countries, have been published previously.[21] In brief, adult patients with FAP, a germline pathogenic variant of the *APC* gene, and any of the following on baseline endoscopy were included: 1) intact colon: moderate adenoma burden (100–1000 polyps) being considered for prophylactic surgery; 2) retained rectum or ileal pouch ≥3 years since IRA or IPAA surgery with International Society for Gastrointestinal Hereditary Tumours (InSiGHT) stage 1, 2, or 3 polyposis[23] and excision of any polyp ≥5 mm at baseline; or 3) duodenum with Spigelman stage III or IV polyposis or stage III or IV that has been downstaged to Spigelman stage I or II within the past 6 months. The stratification was based on disease state. Patients with major personal cardiovascular risk factors or using hearing aids were excluded from the study.[24] Patients were randomly assigned 1:1:1 to receive either 750 mg eflornithine, 150 mg sulindac, or both orally once daily for up to 48 months. In the monotherapy arms, patients received a placebo pill to mimic the medication they were not receiving. Patients underwent upper and lower GI endoscopy every 6 months to assess disease status; endoscopies were conducted by endoscopists experienced in FAP and blinded to the treatment. This post hoc analysis was undertaken on patients with a partial or fully intact LGI tract (an anatomical grouping) and excluded 13 patients who had a permanent ileostomy and focused on the treatment effect on time to first LGI disease progression event.

End Points

For the current analysis, the primary efficacy end point, a composite measure of time to first disease progression in the LGI tract, was defined as the endoscopist's recommendation for 1) the need for colectomy or proctocolectomy; 2) the need for proctectomy or pouch excision, 3) endoscopic excision of any polyp ≥10 mm in size in the rectum or pouch, and/or 4) diagnosis of high-grade dysplasia or cancer in the rectum or pouch. The "need for surgery" was based on recommendations by experienced FAP endoscopists who had received standardization and

calibration training. In the absence of cancer, patients were not required to undergo surgery as part of the trial and could choose if and when they would have their operation. Patients were monitored for adverse events (AEs) and serious AEs, and all patients are reported who received at least 1 dose of study drug in accordance with National Cancer Institute's Common Terminology Criteria for Adverse Events Version 4.0.[25] Treatment-emergent AEs (TEAEs) were defined as any AE occurring after administration of the first dose of study drug and through 30 days after the last dose of study drug.

Statistical Analysis

The composite primary end point, time to any polyposis site prespecified disease progression event in the combination treatment compared with each drug alone, was determined for the intent-to-treat population using a 2-sided, stratified, log-rank test using the score method ($\alpha = 0.05$) and reported graphically as Kaplan-Meier survival curves.[22] The HR of the probability of having a disease progression event was derived from the Cox proportional analysis, and the score method was used to derive the 95% CI for the HR for each comparison. Patients with upper GI disease progression end points without a concurrent LGI disease progression end point were censored at the time when the upper GI event was reported. An additional analysis also censored patients with endoscopic resection of large adenomas to separate polyp removal from the more clinically significant disease progression with need for surgery.

RESULTS

Patients

The LGI subpopulation (n = 158) included 38 patients with intact colons, 53 whose status was postcolectomy with IRA, and 67 whose status was postproctocolectomy with IPAA. One patient who was randomly assigned to receive eflornithine but was not treated was included in the intent-to-treat population for efficacy analysis, but the patient was not included in the safety population. Baseline patient demographics and disease characteristics were generally comparable across the 3 treatment arms; combination (n = 54), sulindac (n = 53), and eflornithine (n = 51; Table 1); the proportion of patients who had undergone an IPAA was greater in the combination arm than in the monotherapy arms. More patients with retained rectum or pouch in the combination arm had advanced polyposis burden than in the monotherapy arms.

Efficacy

Disease progression in the LGI tract occurred in 2 of 54 (3.7%), 9 of 53 (17.0%), and 10 of 51 (19.6%) patients in the combination, sulindac, and eflornithine arms, corresponding to risk reductions for LGI interventions of 80% (HR, 0.20; 95% CI, 0.05–0.8; $p = 0.020$) and 83% (HR, 0.17; 95% CI, 0.04–0.69; $p = 0.010$) between combination and sulindac or eflornithine in a time-to-event analysis (Table 2; Fig. 1).

When patients who underwent endoscopic excision of polyps ≥10 mm in size were censored (n = 6, two in each treatment arm), none of the patients in the combination arm progressed to a need for LGI surgery for up to 48 months compared with 7 (13.2%) and 8 (15.7%) patients in the sulindac and eflornithine arms (Table 2; Fig. 2). These data corresponded to risk reductions for the need for LGI surgery approaching 100% between combination and either monotherapy with HR = 0.00 (95% CI, 0.00–0.48; $p = 0.005$) for combination versus sulindac and HR = 0.00 (95% CI, 0.00–0.44; $p = 0.003$) for combination versus eflornithine.

In the intact colon group (n = 38), none of the patients in the combination arm (n = 13) had disease progression, indicating the need for a colectomy or proctocolectomy for up to 48 months compared with 4 (30.8%) and 3 (25.0%) patients in the sulindac (n = 13) and eflornithine (n = 12) arms (Table 2; Fig. 3). These data corresponded to risk reductions for the need for LGI surgery approaching 100% between combination and either monotherapy with HR = 0.00 (95% CI, 0.00–1.08; $p = 0.06$) for combination versus sulindac and HR = 0.00 (95% CI, 0.00–1.38; $p = 0.10$) for combination versus eflornithine.

In the group of patients who had an IRA or IPAA (n = 120), 2 of 41 (4.9%) patients in the combination arm showed disease progression during the study compared with 5 of 40 (12.5%) and 7 of 39 (17.9%) patients in the sulindac and eflornithine arms (Table 2). These data corresponded to risk reductions for the need for LGI surgery and excision of polyps ≥10 mm in size with or without high-grade dysplasia of 64% (HR, 0.36; 95% CI, 0.08–1.60; $p = 0.20$) between combination and sulindac treatment, and 76% (HR, 0.24; 95% CI, 0.56–1.01; $p = 0.05$) between combination and eflornithine treatment. When the patients in this group who only underwent excision of polyps ≥10 mm in size with or without high-grade dysplasia (n = 6, two in each treatment arm) were censored, no patient in the combination arm had the need for LGI surgery for up to 48 months compared with 3 (7.5%) and 5 (12.8%) in the sulindac and eflornithine arms (Table 2). These data corresponded to risk reductions for LGI interventions approaching 100% between combination and either monotherapy with HR = 0.00 (95% CI, 0.00–1.17; $p = 0.07$) for combination versus sulindac and HR = 0.00 (95% CI, 0.00–0.72; $p = 0.02$) for combination versus eflornithine.

When postcolectomy patients who had severe disease in the retained rectum or pouch (InSiGHT stages 2 and 3) at baseline were evaluated for disease progression events (need for surgery or removal of a polyp ≥10 mm in size with or without high-grade dysplasia), only 1 of

23 (4.3%) patients in the combination arm had disease progression compared with 5 of 23 (21.7%) patients in the sulindac arm and 6 of 18 (33.3%) patients in the eflornithine arm.

Safety

Safety data for the whole study population have been reported previously in detail.[22] The safety profiles were comparable between the treatment arms in the LGI safety population (Table 3). Most TEAEs were mild to moderate in severity and resolved with minimal intervention. Overall, nausea (18.5%), headache (14.6%), vomiting (13.4%), abdominal pain (12.1%), diarrhea (12.1%), nasopharyngitis (11.5%), fatigue (10.8%), and upper respiratory tract infection (10.8%) were the most common TEAEs reported. Serious TEAEs for small-intestinal obstruction were reported by 2 patients each in the combination (3.7%) and sulindac (3.8%) arms. Nine (16.7%), 6 (11.3%), and 4 (7.8%) patients in the combination, sulindac, and eflornithine arms discontinued treatment because of AEs.

DISCUSSION

The main goals of treatment for patients with FAP are to prevent cancer and maintain patient QoL.[7,8,26] This can be accomplished by minimizing increases in adenoma number and size and the development of advanced adenomas.[7,8,26] Such a strategy will provide opportunities to delay or avoid life-altering surgery and associated reduced QoL.[27] Prevention of advanced adenomas has been recognized as an appropriate end point in pharmacotherapy trials.[22,28,29]

TABLE 1. Baseline patient demographics and disease characteristics of the LGI study population

Characteristic	*Combination (n = 54)*	*Sulindac (n = 53)*	*Eflornithine (n = 51)*
Male, n (%)	33 (61.1)	35 (66.0)	25 (49.0)
Age, y	37.4 (13.4)	37.1 (13.4)	38.1 (14.5)
Race, n (%)			
White	46 (85.2)	46 (86.8)	48 (94.1)
Black	6 (11.1)	3 (5.7)	1 (2.0)
Other	2 (3.7)	4 (7.5)	2 (3.9)
BMI, kg/m^2	27.2 (6.0)	27.2 (5.6)	28.2 (6.3)
Surgical status, n (%)			
Intact colon	13 (24.1)	13 (24.5)	12 (23.5)
InSiGHT stage			
Stage 0/1	11	10	10
Stage 2/3	2	3	1
Stage 4	0	0	1
Polyp number			
1–100	2	4	2
101–1000	11	9	9
>1000	0	0	1
Polyp ≥10 mm	5	10	6
Colectomy with IRA	13 (24.1)	19 (35.8)	21 (41.2)
InSiGHT stage			
Stage 0/1	3	6	11
Stage 2/3	10	13	9
Stage 4	0	0	1
Polyp number			
0–10	3	3	4
11–25	0	4	8
>25	10	12	9
Polyp ≥10 mm	10	7	10
Proctocolectomy with IPAA	28 (51.9)	21 (39.6)	18 (35.3)
InSiGHT stage			
Stage 0/1	15	11	9
Stage 2/3	13	10	9
Stage 4	0	0	0
Polyp number			
0–10	10	7	9
11–25	7	6	3
>25	11	8	6
Polyp ≥10 mm	8	9	5

Data presented as mean (SD) unless otherwise stated.
InSiGHT = International Society for Gastrointestinal Hereditary Tumours; IRA = ileorectal anastomosis; LGI = lower gastrointestinal.

TABLE 2. Analysis of LGI disease progression in LGI tract study population

Patients/statistic	*Combination*	*Sulindac*	*Eflornithine*
LGI ITT population	54 (100)	53 (100)	51 (100)
FAP-related LGI disease progression	2 (3.7)	9 (17.0)	10 (19.6)
Need for LGI surgery	0 (0)	6 (11.3)[a]	8 (15.7)
Excision of ≥10 mm adenomas ± HGD	2 (3.7)	3 (3.8)	2 (3.9)
Intact colon subgroup	13 (100)	13 (100)	12 (100)
FAP-related LGI disease progression	0	4 (30.8)	3 (25.0)
Need for LGI surgery	0 (0)	4 (30.8)	3 (25.0)
Combined IRA and IPAA subgroups	41	40	39
FAP-related LGI disease progression	2 (4.9)	5 (12.5)	7 (17.9)
Need for LGI surgery	0 (0)	2 (5.0)	5 (12.8)
Excision of ≥10 mm adenomas ± HGD	2 (4.9)	3 (7.5)	2 (5.1)
IRA subgroup	13 (100)	19 (100)	21 (100)
FAP-related LGI disease progression	1 (7.7)	3 (15.8)	4 (19.9)
Need for LGI surgery	0 (0)	1 (5.3)[a]	3 (14.3)
Excision of ≥10 mm adenomas ± HGD	1 (7.7)	2 (10.5)	1 (4.8)
IPAA subgroup	28 (100)	21 (100)	18 (100)
FAP-related LGI disease progression	1 (3.6)	2 (9.5)	3 (16.7)
Need for LGI surgery	0 (0)	1 (4.8)	2 (11.1)
Excision of ≥10 mm adenomas ± HGD	1 (3.6)	1 (4.8)	1 (5.6)

Data presented as n (%).
FAP = familial adenomatous polyposis; HGD = high-grade dysplasia; IRA = ileorectal anastomosis; ITT, intent-to-treat; LGI, lower gastrointestinal.
[a]One patient had need for surgery and excision of ≥10 mm adenoma ± HGD.

Our analysis of the data for patients with at least a partially intact LGI tract in the CPP FAP-310 trial demonstrated that they responded very well to combination treatment with sulindac and eflornithine, exhibiting ≥80% reduction in risk for disease progression compared with either drug alone. This benefit with combination therapy was observed despite the much lower than anticipated number of patients exhibiting disease progression in the monotherapy arms. The low numbers of patients with confirmed disease progression precluded calculating the median or mean time to disease progression for all 3 treatment arms of the LGI subpopulation. These data are consistent with previous reports showing that single agent sulindac has limited long-term efficacy in reducing

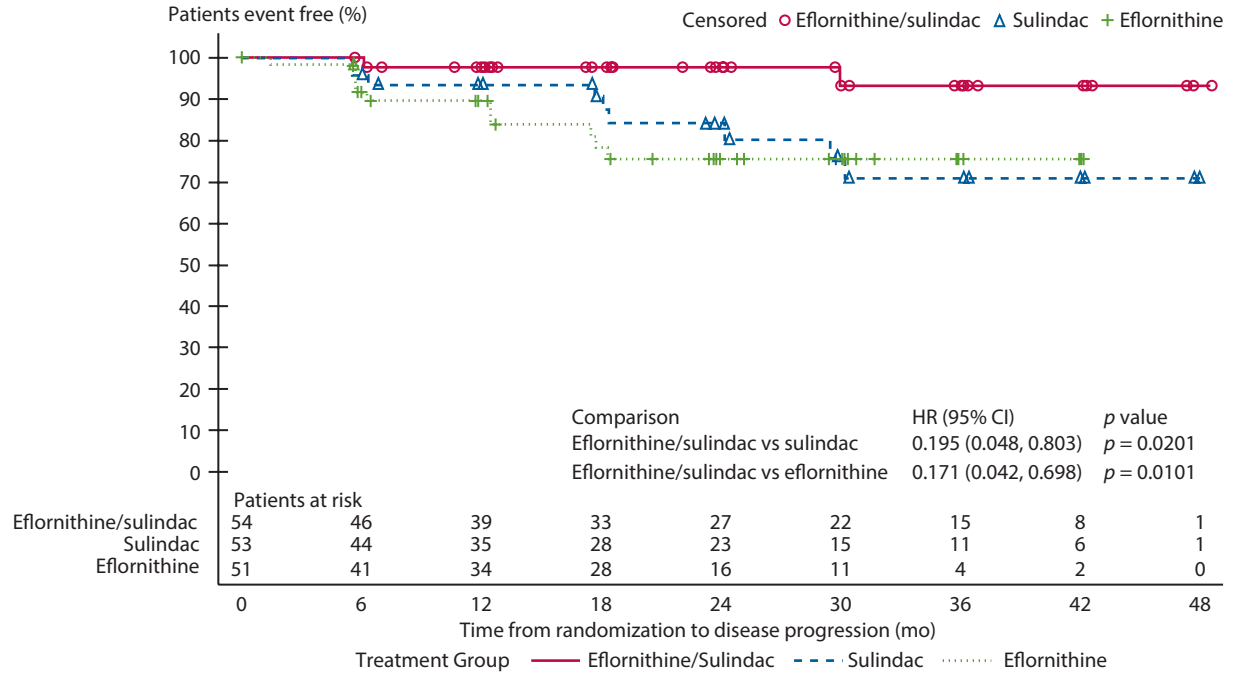

FIGURE 1. Kaplan-Meier plot on time to first LGI disease progression in the LGI study population. LGI = lower gastrointestinal.

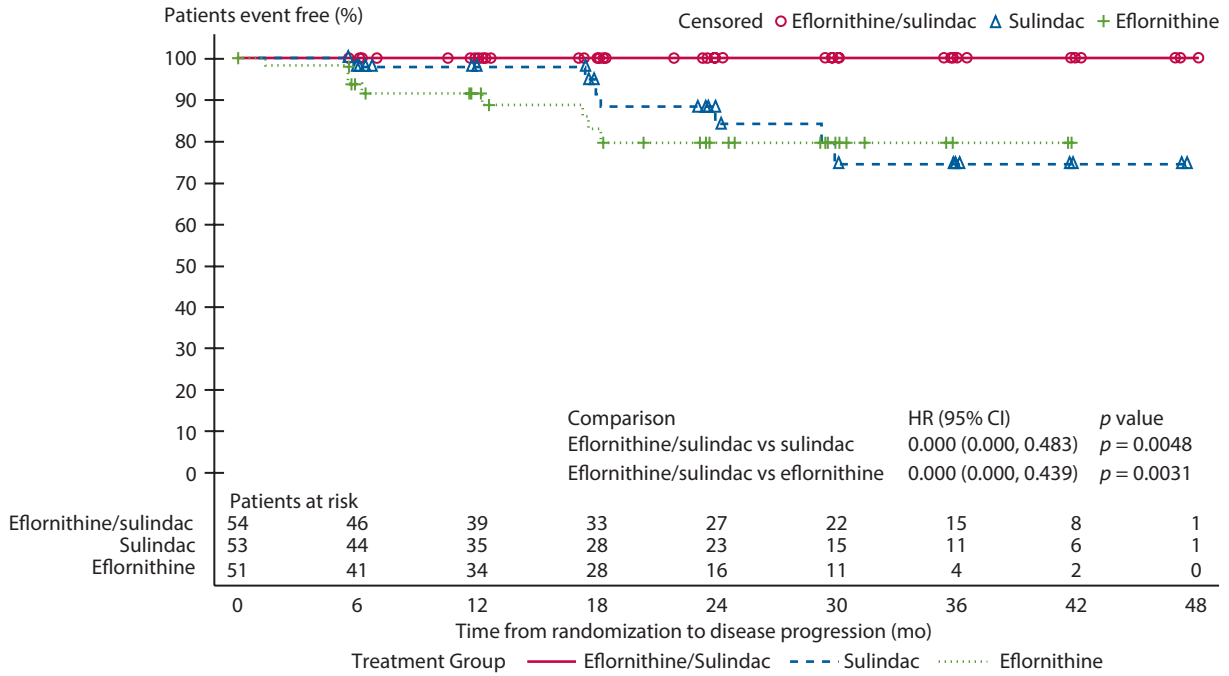

FIGURE 2. Kaplan-Meier plot on time to first LGI disease progression in the LGI study population censored for patients with excisions of ≥10 mm polyps. LGI = lower gastrointestinal.

polyposis in the LGI tract[30,31] and that a combination of eflornithine with nonsteroidal anti-inflammatory drugs reduces global polyp burden.[19]

Under normal conditions, the pool of polyamines is tightly controlled through regulation of synthesis, catabolism, and transport mechanisms mediated through ornithine decarboxylase and spermidine/spermine N1-acetyltransferase 1.[32] In patients with FAP, inactivation of the *APC* gene causes dysregulation of ornithine decarboxylase, increasing its activity and polyamine levels in the colonic mucosa.[32–34] It is known that colonic bacteria are important for sulindac metabolism and the generation of

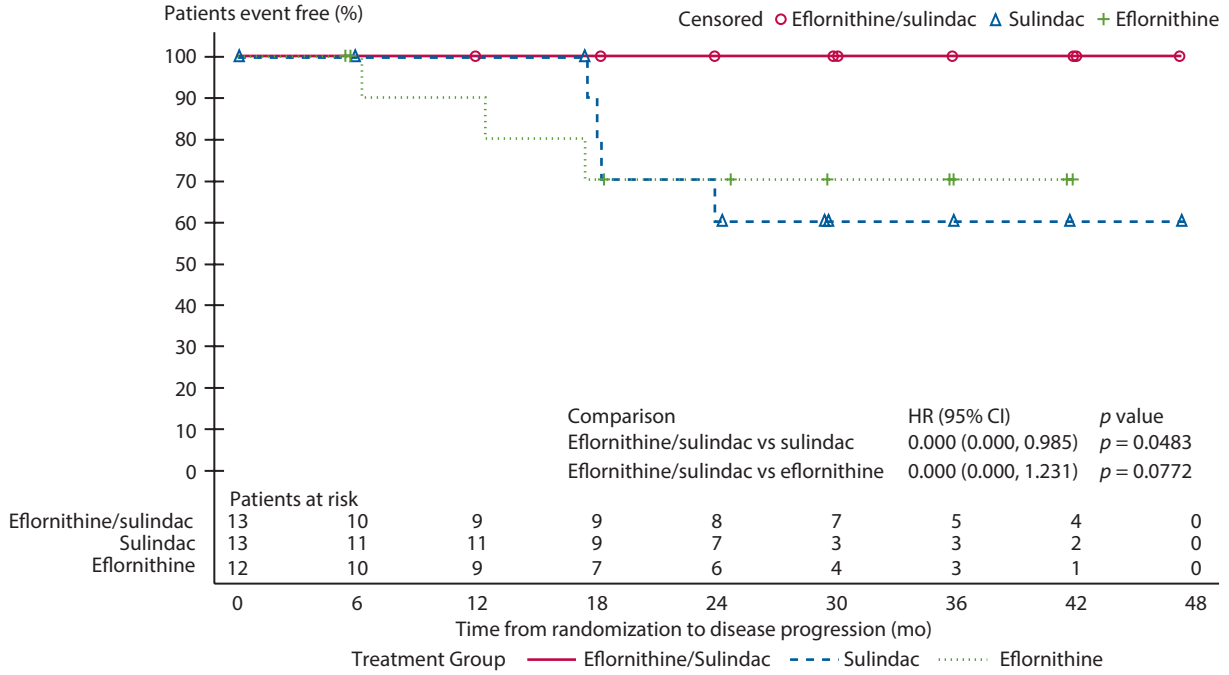

FIGURE 3. Kaplan-Meier plot on time to first lower gastrointestinal disease progression in patients with an intact colon. LGI = lower gastrointestinal.

TABLE 3. Summary of adverse events reported by ≥10% of patients in any treatment arm in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0[25]

Characteristic	*Eflornithine/sulindac (n = 54)*	*Sulindac (n = 53)*	*Eflornithine (n = 50)*
No. of patients reporting TEAEs	50 (92.6)	47 (88.7)	43 (86.0)
No. of patients reporting TEAEs ≥grade 3	13 (24.1)	10 (18.9)	14 (28.0)
No. of patients reporting TESAEs	11 (20.4)	8 (15.1)	11 (22.0)
No. of patients discontinuing due to a TEAE	9 (16.7)	6 (11.3)	4 (7.8)
Death	0	0	0
No. of patients reporting following AEs			
Nausea	12 (22.2)	10 (18.9)	7 (14.0)
Headache	8 (14.8)	11 (20.8)	4 (8.0)
Abdominal pain	8 (14.8)	7 (13.2)	4 (8.0)
Upper respiratory tract infection	8 (14.8)	7 (13.2)	2 (4.0)
Diarrhea	7 (13.0)	5 (9.4)	7 (14.0)
Rectal hemorrhage	7 (13.0)	7 (13.2)	2 (4.0)
Gastroenteritis	7 (13.0)	5 (9.4)	2 (4.0)
Upper abdominal pain	7 (13.0)	1 (1.9)	4 (8.0)
Vomiting	6 (11.1)	2 (3.8)	5 (10.0)
Nasopharyngitis	6 (11.1)	4 (7.5)	8 (16.0)
Hematochezia	6 (11.1)	2 (3.8)	5 (10.0)
Influenza-like illness	5 (9.3)	3 (5.7)	5 (10.0)
Back pain	5 (9.3)	2 (3.8)	5 (10.0)
Oropharyngeal pain	5 (9.3)	1 (1.9)	5 (10.0)
Fatigue	4 (7.4)	7 (13.2)	6 (12.0)
Sinusitis	4 (7.4)	1 (1.9)	5 (10.0)
Cough	3 (5.6)	4 (7.5)	5 (10.0)
Dyspepsia	2 (3.7)	5 (9.4)	5 (10.0)
Tinnitus	2 (3.7)	6 (11.3)	1 (2.0)

Data provided as n (%)
AE = adverse event; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

active metabolites.[35] In clinical settings, studies have demonstrated the efficacy of sulindac in delaying LGI polyposis in patients with FAP who have intact colons and those who have undergone colectomy with IRA.[20] In addition to inhibiting cyclooxygenase and reducing inflammation, sulindac also induces polyamine export and catabolism, thereby decreasing the concentration of polyamines and inhibiting tumor development.[36] In an animal model for FAP, treatment with eflornithine reduced polyposis in the small intestine.[37] Because eflornithine and sulindac independently reduce polyamine levels through inhibition of de novo synthesis and induction of catabolism,[34] they could act additively or synergistically when administered together. In a controlled study involving 375 patients with resected sporadic adenoma at baseline, treatment with a combination of low-dose eflornithine and low-dose sulindac reduced the risk of subsequent metachronous adenomas in the LGI tract by 70% overall, advanced adenomas by 92%, and multiple adenomas by 95%.[18] Both these data and our data support the concept that a combination of eflornithine and sulindac is effective in preventing polyposis progression in the LGI tract.

Although endoscopic excisions of adenomas ≥10 mm in size, one of the disease progression events in our trial, is a measure of disease severity, it is not as clinically significant as the need for LGI surgery. To evaluate the impact of these endoscopic excisions, we censored patients who developed adenomas ≥10 mm during the study. We postulated that having fewer patients on combination therapy than on monotherapy would exhibit disease progression indicating the need for LGI surgery. Although the number of patients with disease progression was much lower than expected for both sulindac and eflornithine, the absence of any patients with disease progression with the need for LGI surgery in the combination arm resulted in a theoretical risk reduction of 100% for patients receiving combination therapy compared with either drug alone, suggesting that combination therapy may be particularly effective in preventing or delaying disease progression requiring LGI surgical interventions. Thus, early detection and initiation of combination therapy may have the greatest benefit to patients by preserving normal anatomy and function and maintaining their QoL.

The major limitation of this analysis, common to all trials in rare diseases, was the small number of patients enrolled despite this study being one of the largest trials on pharmacotherapy in patients with FAP. Potentially, this can be addressed by an additional trial focused on patients with at least a partially intact LGI tract (colon, retained rectum, or ileal pouch) evaluating disease progression in the LGI tract as a primary end point. Because most patients with FAP require colectomy by their late teens

or 20s, it is likely that such a trial will have to include a younger patient population than in the current study to include a sufficient number of patients undergoing precolectomy.[8,38,39] Another limitation was the much lower observed disease progression event rates in the monotherapy arms compared with the expected 70% based on our literature review.[29] Although the combination arm resulted in the expected disease progression event rate of approximately 30%, the event rates in the monotherapy arms were much lower than expected; consequently, we lacked power to estimate the median time to event (disease progression) even in these treatment arms. It is rare for cancers to occur within 10 years among patients whose polyps have been eliminated by sulindac monotherapy.[31,40–42] However, these data may not apply to combination therapy. Nevertheless, an abundance of caution necessitates continued close surveillance and longer-term follow-up of patients on chemoprevention.

The opportunity to delay prophylactic colectomy/proctocolectomy for adolescents and young adults could be beneficial for several reasons. Although prophylactic colectomy remains the standard of care for patients with severe colorectal polyposis that is not amenable to endoscopic control, this can be associated with morbidity, mortality, and lower QoL.[6–10] Regardless of the type of surgery, the risk for desmoid tumors (the second leading cause of FAP-related deaths) and serious morbidity increases with each surgery in patients with FAP, particularly those with certain *APC* mutations.[43,44] Both IRA and IPAA also alter patients' bowel habits, resulting in more frequent bowel movements (on average 4 and 6 per day after IRA and IPAA) and a higher risk of nocturnal fecal incontinence.[7,8,26,27] In recent years, laparoscopic methods have improved outcomes with quicker postoperative recovery and reduced impact on reproductive potential. Nevertheless, all colectomies and proctocolectomies are life-altering surgeries with significant comorbidities that often result in reduced QoL.[7,8,26,27] Controlling rectal and pouch polyposis through pharmacotherapy would potentially maintain normal bowel function, avoiding the mucosal scarring associated with polypectomy, avoiding the need for any type of stoma, and minimizing the risk for desmoid disease. Pharmacotherapy with a combination of eflornithine and sulindac will not soon obviate the need for regular endoscopic examinations. Even if such therapy does not replace the need for colectomy, it could offer patients with FAP, especially those who have an intact colon, the opportunity to meaningfully control or delay polyposis progression, giving them more options regarding the timing of surgery and the type of operation that is best for them based on their personal preferences. To our knowledge, this is the first report of sustained delay for up to 48 months of disease progression by using a pharmacotherapy regimen to treat patients with FAP.

CONCLUSIONS

Our data demonstrate a clinically important benefit of combination therapy with eflornithine and sulindac over monotherapy in delaying disease progression in the LGI tract (intact colon/rectum/pouch) in patients with FAP. There were no internal invasive cancers. The combination treatment was well tolerated.

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REFERENCES

1. Waller A, Findeis S, Lee MJ. Familial adenomatous polyposis. *J Pediatr Genet.* 2016;5:78–83.
2. Aihara H, Kumar N, Thompson CC. Diagnosis, surveillance, and treatment strategies for familial adenomatous polyposis: rationale and update. *Eur J Gastroenterol Hepatol.* 2014;26:255–262.
3. Kennedy RD, Potter DD, Moir CR, El-Youssef M. The natural history of familial adenomatous polyposis syndrome: a 24 year review of a single center experience in screening, diagnosis, and outcomes. *J Pediatr Surg.* 2014;49:82–86.
4. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol.* 2015;110:223–263.
5. Ishikawa H, Mutoh M, Iwama T, et al. Endoscopic management of familial adenomatous polyposis in patients refusing colectomy. *Endoscopy.* 2016;48:51–55.
6. McGrath DR, Spigelman AD. In the beginning there was colectomy: current surgical options in familial adenomatous polyposis. *Hered Cancer Clin Pract.* 2004;2:153–160.
7. Altman AM, Hui JYC, Tuttle TM. Quality-of-life implications of risk-reducing cancer surgery. *Br J Surg.* 2018;105:e121–e130.
8. Campos FG. Surgical treatment of familial adenomatous polyposis: dilemmas and current recommendations. *World J Gastroenterol.* 2014;20:16620–16629.
9. Leonard D, Wolthuis A, D'Hoore A, et al. Different surgical strategies in the treatment of familial adenomatous polyposis: what's the role of the ileal pouch-anal anastomosis? *Acta Gastroenterol Belg.* 2011;74:427–434.
10. Smith JC, Schäffer MW, Ballard BR, et al. Adenocarcinomas after prophylactic surgery for familial adenomatous polyposis. *J Cancer Ther.* 2013;4:260–270.
11. Malloy A, Smith RR. Prophylactic surgery for gastrointestinal malignancies. *Transl Gastrointest Cancer.* 2015;4:337–351.
12. M'Koma AE, Herline AJ, Adunyah SE. Subsequent adenomas of ileal pouch and anorectal segment after prophylactic surgery for familial adenomatous polyposis. *World J Colorectal Surg.* 2013;3:art1.
13. Tajika M, Niwa Y, Bhatia V, Tanaka T, Ishihara M, Yamao K. Risk of ileal pouch neoplasms in patients with familial adenomatous polyposis. *World J Gastroenterol.* 2013;19:6774–6783.

14. Babbar N, Gerner EW. Targeting polyamines and inflammation for cancer prevention. *Recent Results Cancer Res.* 2011;188:49–64.
15. 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;328:1313–1316.
16. Labayle D, Fischer D, Vielh P, et al. Sulindac causes regression of rectal polyps in familial adenomatous polyposis. *Gastroenterology.* 1991;101:635–639.
17. 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;80:1618–1619.
18. Meyskens FL Jr, McLaren CE, Pelot D, et al. Difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas: a randomized placebo-controlled, double-blind trial. *Cancer Prev Res (Phila).* 2008;1:32–38.
19. Lynch PM, Burke CA, Phillips R, et al. An international randomised trial of celecoxib versus celecoxib plus difluoromethylornithine in patients with familial adenomatous polyposis. *Gut.* 2016;65:286–295.
20. Kim B, Giardiello FM. Chemoprevention in familial adenomatous polyposis. *Best Pract Res Clin Gastroenterol.* 2011;25:607–622.
21. Burke CA, Dekker E, Samadder NJ, Stoffel E, Cohen A. Efficacy and safety of eflornithine (CPP-1X)/sulindac combination therapy versus each as monotherapy in patients with familial adenomatous polyposis (FAP): design and rationale of a randomized, double-blind, Phase III trial. *BMC Gastroenterol.* 2016;16:87.
22. Burke CA, Dekker E, Lynch P, et al. Eflornithine plus sulindac for prevention of progression in familial adenomatous polyposis. *N Engl J Med.* 2020;383:1028–1039.
23. Lynch PM, Morris JS, Wen S, et al. A proposed staging system and stage-specific interventions for familial adenomatous polyposis. *Gastrointest Endosc.* 2016;84:115–125.e4.
24. Zell JA, Pelot D, Chen WP, McLaren CE, Gerner EW, Meyskens FL. Risk of cardiovascular events in a randomized placebo-controlled, double-blind trial of difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas. *Cancer Prev Res (Phila).* 2009;2:209–212.
25. National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE) v4.0.* Bethesda, MD: National Institutes of Health; 2010. Accessed on January 15, 2019. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.
26. Andrews L, Mireskandari S, Jessen J, et al. Impact of familial adenomatous polyposis on young adults: quality of life outcomes. *Dis Colon Rectum.* 2007;50:1306–1315.
27. Pappou EP, Kiran RP. The failed J pouch. *Clin Colon Rectal Surg.* 2016;29:123–129.
28. Winawer SJ, Zauber AG. The advanced adenoma as the primary target of screening. *Gastrointest Endosc Clin N Am.* 2002;12:1–9.
29. Keller JJ, Giardiello FM. Chemoprevention strategies using NSAIDs and COX-2 inhibitors. *Cancer Biol Ther.* 2003;2(4 suppl 1):S140–S149.
30. Giardiello FM. Sulindac and polyp regression. *Cancer Metastasis Rev.* 1994;13:279–283.
31. Winde G, Schmid KW, Brandt B, Müller O, Osswald H. Clinical and genomic influence of sulindac on rectal mucosa in familial adenomatous polyposis. *Dis Colon Rectum.* 1997;40:1156–1168.
32. Gerner EW, Meyskens FL Jr. Polyamines and cancer: old molecules, new understanding. *Nat Rev Cancer.* 2004;4:781–792.
33. Giardiello FM, Yang VW, Hylind LM, et al. Primary chemoprevention of familial adenomatous polyposis with sulindac. *N Engl J Med.* 2002;346:1054–1059.
34. Gerner EW, Bruckheimer E, Cohen A. Cancer pharmacoprevention: targeting polyamine metabolism to manage risk factors for colon cancer. *J Biol Chem.* 2018;293:18770–18778.
35. Strong HA, Warner NJ, Renwick AG, George CF. Sulindac metabolism: the importance of an intact colon. *Clin Pharmacol Ther.* 1985;38:387–393.
36. Babbar N, Gerner EW. Polyamines as modifiers of genetic risk factors in human intestinal cancers. *Biochem Soc Trans.* 2003;31:388–392.
37. Erdman SH, Ignatenko NA, Powell MB, et al. APC-dependent changes in expression of genes influencing polyamine metabolism, and consequences for gastrointestinal carcinogenesis, in the Min mouse. *Carcinogenesis.* 1999;20:1709–1713.
38. Tudyka VN, Clark SK. Surgical treatment in familial adenomatous polyposis. *Ann Gastroenterol.* 2012;25:201–206.
39. Warrier SK, Kalady MF. Familial adenomatous polyposis: challenges and pitfalls of surgical treatment. *Clin Colon Rectal Surg.* 2012;25:83–89.
40. Lynch HT, Thorson AG, Smyrk T. Rectal cancer after prolonged sulindac chemoprevention. A case report. *Cancer.* 1995;75:936–938.
41. Niv Y, Fraser GM. Adenocarcinoma in the rectal segment in familial polyposis coli is not prevented by sulindac therapy. *Gastroenterology.* 1994;107:854–857.
42. Utech M, Brüwer M, Buerger H, Tübergen D, Senninger N. Rectal carcinoma in a patient with familial adenomatous polyposis coli after colectomy with ileorectal anastomosis and consecutive chemoprevention with sulindac suppositories. *Chirurg.* 2002;73:855–858.
43. Gurbuz AK, Giardiello FM, Petersen GM, et al. Desmoid tumours in familial adenomatous polyposis. *Gut.* 1994;35:377–381.
44. Calvert GT, Monument MJ, Burt RW, Jones KB, Randall RL. Extra-abdominal desmoid tumors associated with familial adenomatous polyposis. *Sarcoma.* 2012;2012:726537.