Phase III Randomized Study of Two Fluorouracil Combinations With Either Interferon Alfa-2a or Leucovorin for Advanced Colorectal Cancer

By the Corfu-A Study Group

Purpose: To compare the efficacy and toxicity profiles of a combination of fluorouracil (5-FU) with recombinant human interferon alfa-2a (Roferon-A; Hoffman La-Roche AG, Basel, Switzerland) versus the combination of 5-FU with leucovorin (LV) in the treatment of advanced colorectal cancer.

Patients and Methods: A total of 496 previously untreated colorectal cancer patients were randomized to receive either Roferon-A (9 MIU) subcutaneously three times per week, with 5-FU (750 mg/m²/d) by continuous intravenous (IV) infusion (CIV) on days 1 to 5, then, after a 9-day hiatus, as a weekly IV bolus at the same dose (IFN/5-FU); or LV (200 mg/m²/d) by IV infusion plus 5-FU (370 mg/m²/d) by IV bolus on days 1 to 5, repeated every 4 weeks (LV/5-FU).

Results: There were no significant differences between IFN/5-FU and LV/5-FU in the overall response rate (21% v 18%), duration of response (7.3 v 6.2 months), or survival time (median, 11.0 v 11.3 months). Toxicity profiles differed; constitutional symptoms and myelosuppression were more frequent and more severe with IFN/5-FU, and gastrointestinal symptoms with LV/5-FU. More patients interrupted treatment for adverse events (AEs) with IFN/5-FU than with LV/5-FU. Five treatment-related deaths occurred with each regimen.

Conclusion: The combination IFN/5-FU produced response rates, response durations, and survival times similar to those with LV/5-FU. Biochemical modulation of 5-FU by either IFN or LV appears to result in equivalent efficacy; however, fewer patients were able to tolerate the specified IFN/5-FU combination used in this study.

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COLORECTAL CANCER is one of the most common malignancies in the Western industrial countries, with more than 300,000 new cases diagnosed each year.[1] Historically, the most widely used chemotherapeutic agent has been fluorouracil (5-FU). As a single agent, or in combinations with other cytotoxics, the overall response in advanced colorectal cancer is in the range of 17% to 24%, with a median survival time of approximately 11 months.[2-4]

Among various attempts to improve the results of therapies based on 5-FU, experimental studies indicated that the reduced folate leucovorin (LV) increased the cytotoxicity of 5-FU.[5-8] Early phase I and II studies[9,10] suggested enhanced response to 5-FU with LV, and several prospective controlled randomized trials with LV/5-FU combinations have reported higher response rates,[11-15] increases in overall survival,[13,14] and trends toward longer survival[15] than obtained with 5-FU alone.

An alternative approach was suggested by preclinical data that indicated synergy between 5-FU and interferon (IFN).[16-19] Although the mechanism of interaction between IFN and 5-FU remains unclear, several possible modes have been proposed.[20] These include effects at the level of the target enzyme, thymidine synthetase (TS),[21,22] and variable effects on 5-FU pharmacokinetics by both IFN and LV.[23-27]

In a pilot study of eight previously untreated patients with advanced colon cancer treated with 5-FU combined with recombinant interferon alfa-2a (rIFNα-2a), seven patients (87.5%) experienced a major response.[28] A fol-low-up study of 30 patients with advanced colorectal carcinoma using the same treatment regimen reported a 76% objective response rate in 17 previously untreated patients, but no major response in 13 patients previously treated with 5-FU combined with either LV or methotrexate.[29]

The objectives of the present phase III study were to compare the efficacy and toxicity of a combination of 5-FU plus rIFNα-2a (at 9 MIU three times per week) with that of the combination of 5-FU plus LV in the treatment of patients with advanced colorectal cancer.

PATIENTS AND METHODS

Patient Selection and Randomization

Patients 18 to 80 years of age with advanced, histologically confirmed colorectal carcinoma and objectively measurable tumors were enrolled onto the study. The only permitted prior therapies were surgery (at least 4 weeks earlier) and radiotherapy (if at least 30 days after treatment termination, if the indicator lesions lay outside the radiation port, and if collectively < 25% of bone marrow sites were irradiated). Excluded from the study were patients with the

presence of osseous metastases as the sole tumor site, serious concurrent medical illness, history of other malignancies, Karnofsky performance status less than 60, and abnormal hematologic, liver, and renal laboratory values (granulocytes $< 1.5 \times 10^9/L$, platelets $< 100 \times 10^9/L$, bilirubin level > 1.25 times the upper normal limit, and serum creatinine concentration $> 145 \mu mol/L$). Informed consent was obtained from all patients before commencing treatment, and the study was approved by the institutional review boards of the participating centers.

Computer-generated randomization lists were produced from the coordinating center and supplied to each participating study center. Treatments were assigned randomly to the eligible patients by the use of individual sealed envelopes opened by investigators according to the sequence of enrollment. The trial was conducted as an open-label study.

Treatment Regimens

The treatment regimens consisted of 5-FU with either rIFNα-2a (Roferon-A; Hoffmann La-Roche AG, Basel, Switzerland) or LV. The 5-FU dosage and schedule differed between the two regimens. With the IFN/5-FU combination, the dosage schedule reported by Wadler et al[29] was used. The first cycle (4 weeks) consisted of 5-FU (750 mg/m²/d) administered by a continuous intravenous infusion (CIV) for the first 5 days, and then after a 9-day interval, as a weekly bolus intravenous (IV) injection at the same dose. For subsequent cycles, 5-FU (750 mg/m²) was administered as a weekly bolus IV injection. Roferon-A (9 MIU) was administered subcutaneously (SC) 3 days per week throughout the treatment period. With the LV/5-FU combination, the dosage schedule reported by Erlichman et al[13] was used. A cycle of treatment (4 weeks) consisted of LV (200 mg/m²/d) administered as a 10-minute IV infusion followed 5 minutes later by 5-FU (370 mg/m²/d) administered as an IV bolus injection on days 1 to 5 of the first week of the treatment cycle.

Dose modifications were made during therapy based on clinical and laboratory toxicity criteria using World Health Organization (WHO) grades for toxicity.[30] With IFN/5-FU, subsequent 5-FU doses were withheld for all grade 2 and 3 toxicities until recovery and restart at 66% of the full dose. The Roferon-A dose was reduced by 33% for all grade 3 toxicities, without interruption of therapy, except in the cases of grade 3 diarrhea, stomatitis, CNS toxicity or myelosuppression, for which it was temporarily discontinued until recovery. If toxicity resolved, the dose of Roferon-A was increased to the previous level. Patients were withdrawn from the study in the event of any recurrence of grade 2 or greater toxicity. With LV/5-FU, dose modifications for 5-FU were made primarily for myelosuppression and gastrointestinal toxicities. Subsequent doses of 5-FU were reduced by 70 mg/m²/d for grade 2 and 3 toxicities. There was no dose modification for LV. The 5-FU dose could be escalated by 15% if a patient completed a previous cycle of treatment without experiencing myelosuppression, stomatitis, or diarrhea. With either regimen, patients with grade 4 toxicities (except for nausea, vomiting, alopecia, and anemia) were withdrawn from the study.

Concomitant radiotherapy for bone pain was allowed if the irradiated field was localized. Radiotherapy to an indicator lesion precluded the site from evaluations of tumor response. Corticosteroids were allowed as antiemetic therapy, but agents that modulated the endocrine or immunologic responses to cancer, and additional antineoplastic drugs, were not permitted. Patients who achieved a complete response (CR) were treated for a further 12 months, and those

with a partial response (PR) or no change (NC) were treated until disease progression (PD).

Response Criteria

Tumor size was measured by computed tomographic (CT) scan, x-ray, or any other technique that allows retrospective and independent response assessment. Centers were required to be consistent with respect to the method of assessment for each patient. Measurements were made at baseline and every 8 weeks thereafter. Tumor assessment and measurement adhered strictly to WHO criteria.[30] The measurement of bone metastases was not used as a parameter of tumor response. A CR was defined as the disappearance of all detectable disease on two consecutive evaluations. A PR was defined as a $\geq$ 50% reduction of the summed products of the two greatest diameters of all measurable tumors, with no new lesions appearing and none progressing for at least 4 consecutive weeks. NC was defined as a less than 25% increase or less than 50% decrease of the summed tumor size, as defined under PR, throughout the treatment period. PD was defined as a $\geq$ 25% increase of the summed tumor size or the appearance of new lesions. On each assessment occasion, the patient's best overall response to that date was determined (as defined earlier), together with the date of onset and duration. All CR and PR decisions were reviewed by an independent external panel of oncologists and radiologists blinded to treatment received. In addition, a random sample of nonresponders was reviewed by the external panel.

Survival was determined from the date of first treatment until death or until the patient was last seen alive. Time to PD was determined as the number of days between the date of first treatment and the date of PD was first observed.

Statistical Considerations and Analysis

Sample size. Based on the study reported by Wadler et al,[29] the sample-size calculation assumed a 50% response rate with IFN/5-FU and a 30% rate with LV/5-FU. With at least 130 assessable patients entered onto each arm, a χ^2 test would have a power of 80%. The sample size was then adjusted on the further assumption that approximately 20% of patients would not be assessable for efficacy. An interim analysis for response rate only was planned and performed after a total of 238 patients were enrolled. In the event of an unexpectedly high response rate in the IFN/5-FU arm, the study would have been stopped. The significance level α was set at 2.5% for the χ^2 test at the interim analysis and also at the final analysis so that the overall significance level could be kept at 5%.

Analysis. Demographic data of the two patient groups were summarized (median and range). The principal efficacy parameters for comparing the two regimens were patient survival and response rates. The following statistical procedures were applied to the efficacy variables: the Kaplan-Meier product-limit method[31] to estimate survival, time to progression, time to response, and duration of response; the log-rank test[32] to compare the two treatment groups on the foregoing times and durations; and the Mantel-Haenszel χ^2 statistic[33] to compare the best clinical responses. Patients were censored as follows: patients with an unknown date of death were censored on the last known day of life; nontreated patients with no further information were censored on day 1. For analysis of time to response, nonresponders were censored at a time to response later than that of responders, regardless of their last date of evaluation. In the analysis of time to PD, patients who progressed (ie, not CR,

PR, or NC) were considered as having progressed on day 1. Prognostic factors on response were tested by a logistic regression. Prognostic factors for survival were tested by Cox regression analysis.[34] The following statistical procedures were applied to the toxicity variables: the number of patients who experienced at least one adverse event (AE) within a given body system was compared between the two treatment groups using Fisher's exact test, and the distribution of patients over sequential grades of severity was compared between the two treatment groups using the Cochran-Armitage test for trend.[35-37] In addition, for the worst degree of relationship of AEs to treatment, the distribution of patients over sequential degrees of the relationship was compared by the Cochran-Armitage test. For clinical laboratory data, the distribution of patients over sequential WHO grades was compared between the two treatment groups using the Cochran-Armitage test for trend. Differences with a P value less than .05 (two-tailed) were regarded as significant unless otherwise specified.

Quality Assurance

All patients entered onto the study were monitored on a monthly basis according to protocol, with special regard to serious and unexpected AEs. All data on patient demographics, tumor response, drug dispensing and administration, toxicity, and survival were verified against patient and hospital records by the sponsor. Data on tumor responses (including radiologic investigations) of all responders and of a large sample of nonresponders were evaluated by an independent panel of oncologists and radiologists who had no involvement in the study. The panel was unaware of the treatments allocated to patients.

Survival was determined from the date of first treatment until death or until June 1992 (clinical data cut-off) for surviving patients. The time to PD was the number of days between the date of first treatment and the date PD was first observed.

RESULTS

Patient Accrual and Demographics

From January 1990 to April 1991, a total of 496 patients from 42 centers in Europe, Canada, Australia, and Brazil were enrolled onto the study. The final sample size was due to completion of contractual commitments. Of this total, 246 were randomized to receive IFN/5-FU and 250 to LV/5-FU. Four patients were ineligible: one on IFN/5-FU had a previous melanoma and three on LV/5-FU had received previous 5-FU treatment. The results for the efficacy analysis reported here refer to all 492 eligible, randomized patients. In the safety analysis population, there were 486 patients, as 10 patients (two assigned to IFN/5-FU and eight to LV/5-FU) did not receive therapy. The principal demographic characteristics of the two patient groups in the intent-to-treat analysis are listed in Table 1. The composition of the groups was equally matched.

Responses

The best responses of patients who received the two treatment regimens are listed in Table 2. The overall ob-

Table 1. Demographic Data

Variable	IFN/5-FU (n = 245)		LV/5-FU (n = 247)	
	No.	%	No.	%
Sex				
Male	144	59	157	64
Female	101	41	90	36
Age (years)				
Medium	60.0		62.0	
Range	27.0-79.0		27.0-80.0	
Weight (kg)				
Medium	66.3		69.0	
Range	37.0-104.0		42.0-195.0	
Height (cm)				
Medium	168.0		169.0	
Range	146.0-192.0		148.0-195.0	
Body-surface area (m²)				
Medium	1.8		1.8	
Range	1.3-2.3		1.4-2.4	
Karnofsky performance status (%)				
Medium	90		90	
Range	60-100		60-100	

jective response rates of 21% (IFN/5-FU) and 18% (LV/5-FU) were not significantly different ($P = .57$). The time to response, defined as the time from the start of treatment to the first record of the patient's best response (CR or PR), did not differ significantly between the regimens ($P = .50$), with the probability of a response reaching a plateau at approximately 4 months. The median durations of overall responses (CRs and PRs) for patients treated with IFN/5-FU (7.3 months) and with LV/5-FU (6.2 months) were not significantly different ($P = .80$). The median times to PD for IFN/5-FU and LV/5-FU were not significantly different at 3.7 and 4.0 months, respectively ($P = .92$). The frequencies of responses by sites of disease did not differ appreciably between the two treatment regimens. A logistic regression analysis was performed on the prognostic factors with the following variables: age, sex, Karnofsky status, carcinoembryonic antigen, location of metastases (liver and lung only), and treatment group. The only factor with a significant relationship to response (CR and PR) was Karnofsky performance status ($P = .009$).

Cumulative Dose of 5-FU

Due to the different 5-FU doses and schedules for the two treatment arms, a higher average cumulative dose of 5-FU was actually administered per patient with IFN/5-FU (28.62 g/m²) than with LV/5-FU (21.04 g/m²) during the study. Within the respective regimens, the ratio of the 5-FU dose received versus planned doses of 5-FU (Fig

Table 2. Overall Tumor Response

Tumor Response	IFN/5-FU (n = 245)		LV/5-FU (n = 247)	
	No.	%	No.	%
CR	7	3	5	2
PR	43	18	40	16
NC	109	44	109	44
PD*	62	25	74	30
Not treated	2	1	8	3
Not assessable†	22	9	11	4
Overall response	50	20	45	18

*Includes mixed response, early progression, and early death.

†Inadequate follow-up data available to evaluate tumor response.

1), was greater with the LV/5-FU regimen than the IFN/5-FU regimen.

Toxicity and Survival

At the time of the final analysis, 180 patients (37%) had been withdrawn from the study. The most frequent reason for withdrawal was the occurrence of AEs, which resulted in 21% of patients withdrawing from IFN/5-FU and 10% from LV/5-FU, principally during the first 24 weeks of the study. The majority of patients in both treatment regimens experienced at least one AE (99.6% with IFN/5-FU and 97% with LV/5-FU). The major toxicities

Fig 1. Ratio of received v expected 5-FU dose.

Table 3. Patients With Most Prevalent AEs

AE	Toxicity Grades*	IFN/5-FU (n = 244)	LV/5-FU (n = 242)	Lower AE Incidence†
Abdominal pain	1, 2	21	34	IFN/5-FU
	3, 4	6	21	
Constipation	1, 2	21	39	IFN/5-FU
	3, 4	1	8	
Diarrhea	1, 2	109	122	IFN/5-FU
	3, 4	35	45	
Fatigue	1, 2	82	72	LV/5-FU
	3, 4	26	12	
Fever	1, 2	124	61	LV/5-FU
	3, 4	13	8	
Influenza-like symptoms	1, 2	60	5	LV/5-FU
	3, 4	4	0	
Nausea/vomiting	1, 2	130	124	—
	3, 4	15	27	
Shivering	1, 2	29	12	LV/5-FU
	3, 4	4	0	
Somnolence	1, 2	18	3	LV/5-FU
	3, 4	14	1	
Stomatitis	1, 2	108	132	IFN/5-FU
	3, 4	16	23	
Any one of the above AEs	1, 2	138	130	—
	3, 4	96	94	

*Toxicity grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening.

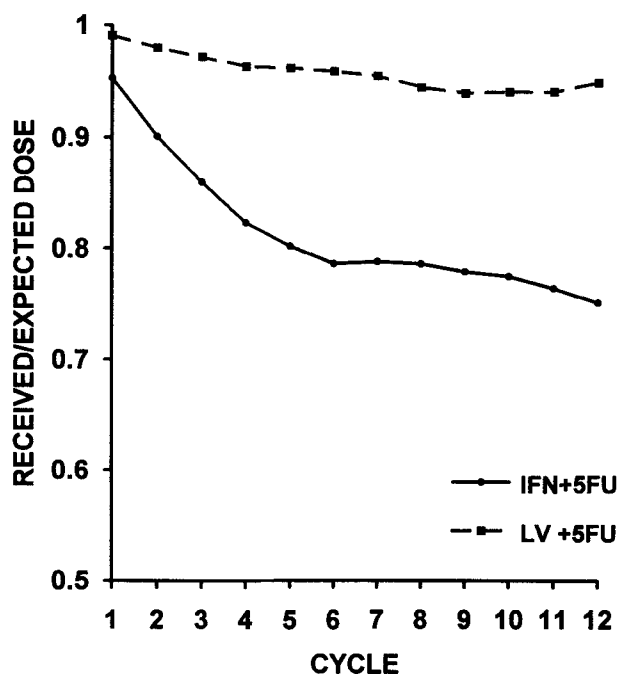†Using the Cochran-Armitage test for trend on all ordered categories (P < .05).

experienced by the patients with each regimen are compared in Table 3 and the clinical and laboratory toxicities are listed in Table 4. In each category, each patient is represented by the worst toxicity experience (WHO grade). There was no significant difference in the overall toxicity between the two regimens in terms of the frequency or severity of AEs, but significantly ($P = .021$) more AEs were considered to be related to IFN/5-FU than to LV/5-FU. The most common toxicities with both regimens were nausea/vomiting, diarrhea, stomatitis, anemia, bone marrow suppression, and increased liver enzymes.

However, IFN/5-FU was characterized by more frequent and more severe systemic disorders (fatigue, fever, influenza-like symptoms, and shivering) and somnolence, which were regarded as possibly or probably related to treatment. In addition, leukopenia and thrombocytopenia (a minority of cases) were significantly ($P = .0001$) more frequent with IFN/5-FU. For some patients, the reduction of leukocytes was severe or life-threatening. Although the IFN/5-FU regimen showed a significant trend ($P = .028$) for higher titers of AST, the difference was not clinically relevant, and there was no difference in the ALT values between the two regimens. In contrast, LV/5-

Laboratory Variable	WHO Grades	IFN/5-FU (n = 244)	LV/5-FU (n = 242)	Lower AE Incidence*
Hemoglobin	1, 2	151	129	—
	3, 4	8	12	
WBC count	1, 2	154	109	LV/5-FU
	3, 4	41	37	
Neutrophil count	1, 2	111	64	—
	3, 4	74	82	
Platelet count	1, 2	57	19	LV/5-FU
	3, 4	7	5	
Alkaline phosphatase	1, 2	112	129	—
	3, 4	14	11	
AST	1, 2	95	80	LV/5-FU
	3, 4	7	4	
ALT	1, 2	68	57	—
	3, 4	4	5	
Any one of the above AEs	1, 2	137	125	—
	3, 4	101	100	

*Using the Cochran-Armitage test for trend on all ordered categories ($P < .05$).

FU was characterized by more frequent and more severe gastrointestinal disorders (abdominal pain, diarrhea, nausea and vomiting, stomatitis, and constipation).

Thirty patients (12%) experienced one or more life-threatening AEs with IFN/5-FU and 37 patients (15%) with LV/5-FU. Of the patients who died during and within 4 weeks after stopping treatment, 36 deaths were attributed to disease, 16 to other causes, and six to unknown causes. There were 10 deaths (five in each regimen) regarded as probably or possibly related to treatment. The number of unrelated deaths was similar in both regimens.

The median overall survival time after a 20-month follow-up period was 11.0 months for patients treated with IFN/5-FU and 11.3 months with LV/5-FU (Fig 2). The median survival time of patients who responded (CR or PR) was 19.3 months with IFN/5-FU and 20.6 months with LV/5-FU.

Neutralizing antibodies to rIFNα-2a were detected in 23 of 226 patients (10%) from whom blood samples were collected.

DISCUSSION

In the past decade, a number of approaches have been tested to improve the activity of 5-FU with the use of biochemical modulators, including LV and IFNs. Several phase II and III trials have shown that biochemical modulation with either LV[38,39] or rIFNα-2a[40] produces higher response rates over 5-FU alone for the treatment of colorectal cancer. However, the present study (the subject of

a previous preliminary report[41]) demonstrated no difference in activity (in terms of overall response, time to response, and duration of response or overall survival) between a combination of rIFNα-2a plus 5-FU and LV plus 5-FU in patients with advanced colorectal cancer.

The overall response rate of 20% for the IFN/5-FU combination in this study was much less than the 76% originally reported by Wadler et al,[29] who used the same dosage schedule. Other phase II studies[42-46] that used the same or similar treatment schedules reported response rates that ranged from 26% to 42%. The lower response rate in this large, international, multicenter, phase III study may largely reflect the relatively unselected nature of the patient population. Furthermore, in the LV/5-FU combination, the overall response rate of 18% was also less than the 33% reported by Erlichman et al.[13] Other randomized trials[11-15,47-51] reported response rates of 15% to 48%. However, when these trials were analyzed in a meta-analysis[52] of 10 studies, an overall response rate of 23% was reported, which is more consistent with the present study.

It has been suggested that perhaps a combination of the three drugs could produce a better response, but recent randomized studies[53,54] showed no improvement in the response rate with the three-drug combination compared with a combination of 5-FU plus LV.

The overall median survival time of approximately 11 months in the present study is consistent with the results of the meta-analysis of 10 studies, which compared the survival of patients with advanced colorectal cancer given various LV/5-FU versus 5-FU regimens.[52] In this meta-analysis, no discernable difference in survival between LV/5-FU regimens and 5-FU alone was found. In patients

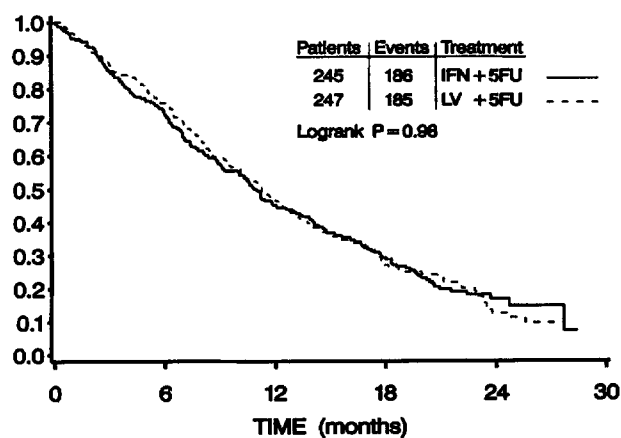| Patients	Events	Treatment
245	186	IFN+5FU
247	185	LV +5FU

Logrank P=0.98

Fig 2. Time from treatment start until death.

with less advanced metastatic disease who did not have measurable tumor masses, modulation of 5-FU by LV might result in a small survival advantage, as reported by Poon et al.[14] The use of IFNα[40] rather than LV,[38,39,52] or even the three drugs combined,[53,54] may not have a significant impact on the survival of patients with advanced colorectal cancer compared with 5-FU alone.

Although a significantly greater number of patients were withdrawn from the IFN/5-FU arm than from the LV/5-FU arm due to AEs, both groups experienced a similar number of grade 3 and 4 toxicities. In addition, although there was a greater reduction in the dose of 5-FU with IFN/5-FU (due to toxicity) than with LV/5-FU, the cumulative dose of 5-FU remained higher with the IFN/5-FU regimen. It was interesting to note that the gastrointestinal toxicity characteristic of 5-FU was less marked with the IFN/5-FU regimen, despite the greater cumulative dose of 5-FU. An analysis of dose-intensity between the two regimens is difficult due to the different dosing schedules. The pattern of AEs with IFN/5-FU is similar to those in other studies using IFN/5-FU combinations[42-46]; however, severe infection, which has been reported often,[44,45] was not a frequent event in the present study.

In conclusion, this study demonstrated that biochemical modulation of 5-FU by either IFN or LV produced comparable efficacy results in advanced colorectal cancer patients with measurable disease. However, since more patients withdrew from the IFN/5-FU arm due to side effects, this combination does not appear to have any major advantages over the LV/5-FU combination. Compared with results reported in the literature, neither of these approaches produces significant survival advantages over 5-FU in this patient population. Cellular targets, in addition to TS inhibition, will need to be considered to make significant progress in the treatment of advanced colorectal cancer. This trial further emphasizes the importance of large, randomized, controlled studies in establishing the true efficacy of new drug combinations.

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APPENDIX

The following members of the Corfu-A Study Group participated in this study: Australia—Sydney: D. Dalley, J. Levi*; Ballarat: D. Bell; Melbourne: M. Green, P. Sherman, J. Zalcberg, A. Zimet; Brisbane: D. Thomson, E. Walpole; Newcastle: S. Ackland, J. Stewart. Austria—Vienna: J. Schüller, U. Fogl, M. Wirth, D. Lutz, J. Salomon; Belgium—Leuven: G. Van Trappen, E. Van Cutsem; Aalst: L. Lepoutre, L. De Facq; Huy: J. Bury, M Reginster. Brazil—Rio de Janeiro: M. Froimtchuk, M. De Lourdes Lopes de Oliveira, A. Scaletzky. Canada—London: W. Kocha, J. Skillings; Winnipeg: B. Weinerman*, T. Shore; Ottawa: J. Maroun, C. Cripps, R. Goel; Montreal: G. Batist, G. Boos. Denmark—Vejle: C. Gadeberg; Aalborg: M. Kjaer*, N. Brunsgaard; Aarhus: A. Jakobsen, J. Mejlholm; Odense: K. Bertelsen, E. Lindegaard Madsen, A. Jorgensen; Esbjerg: E. Sandberg. Finland—Helsinki: S. Pyrhönen, O.-P. Isokangas; Kuopio: R. Johansson, V. Kataja. France—Villejuif: P. Rougier; Bordeaux: Y. Becouarn, R. Brunet; Nice: E. François, M. Namer; Marseille: J. Seitz, M. Giovannini; Lyon: P. Rebattu, Y. Merrouche. Germany—Lüneburg: P. Lankisch, J. Heise; Bochum: B. May, J. Greving; Recklinghausen: C. Sodomann, H. Bergermann; Freiburg: R. Mertelsmann, M. Schupp; Ulm: F. Porzsolt, R. Mayer Steinacker. Italy—Udine: G. Cartei; Milano: E. Bajetta, M. Colleoni; Bologna: E. Pannuti; Vicenza: V. Fosser. Sweden—Eksjo: C. Berg, H. Ravn. Switzerland—Geneva: R. Egeli. United Kingdom—London: P. Guillou, S. Somers, P. Carey; Leeds: J. Primrose, P. Selby, U. Ward. Switzerland—Basel: M. Budde, E.E. Holdener. France—Strasbourg: A. Man*, G. Massimini*, H. Smith, R. Luykx, C. Blaes, A.K.L. Yap*, S. Holmström. United States—Nutley, NJ: L. Cockey.

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