Efficacy

Efficacy Analysis:

Table 20. Efficacy Evaluations and Protocol Specified Statistical Analyses, Study

ENDPOINT	DEFINITION/TEST	STATISTICAL ANALYSIS
Survival	•from date of randomization to death	• analysis on an intent-to-treat basis • Kaplan-Meier estimates • stratified logrank tests[a] with retrospective stratification of prognostic factors
Quality of Life	•comparison of PS •weight change •EORTC QLQ-C30	• statistical analysis plan to be filed before the database is finalized

[a] stratified logrank and Cox modeling for : (1) resistance to prior 5-FU; (2) duration of prior 5-FU therapy. Others to be considered are age, performance status, visceral involvement, number of metastatic sites, intent of and response to prior chemotherapy

***Reviewer's comment**: An unadjusted analysis of survival in the intent-to-treat group was prospectively defined. No formal statistical analysis was planned to compare covariates; however, in the case of heterogeneity, statistical tests were performed by the sponsor to provide the significance level of the observed difference. The following additional evaluations were not mentioned in the protocol but were included in the final study report:*

1. *stratified logrank analysis of other prognostic factors such as sex, weight loss 3 months before baseline, hepatic metastases at inclusion, site of colorectal cancer, hematologic and serum biochemical parameters at baseline such as CEA*
2. *Additional time to event analyses using the Kaplan-Meier method for survival without performance status deterioration, survival without weight loss, pain-free survival, symptom-free survival*

   Note that these analyses were done retrospectively and that these measurements may be adversely affected by imbalances in the timing and frequency of follow-up (as described in Table 16), patient and/or physician reporting behavior, concomitant medications, etc.

Survival

Enrollment to study ended on November 1996 and the cut-off date for data analysis was June 30, 1997 at which time approximately 174 patients (number of deaths required to demonstrate a significant difference in one-year survival rates) had died.

There were 61 (32%) and 14 (16%) living patients in Arms A and B, respectively on the cut-off date. Five patients were lost to follow-up in each arm and censored on the last day of follow-up.

Reviewer's comments: Censoring

A greater proportion of patients in Arm A being alive at the cut-off date (35% vs. 21%) is consistent with the findings of a longer median survival in Arm A.

Review of electronic data confirmed the sponsor's findings above and showed the following additional results:

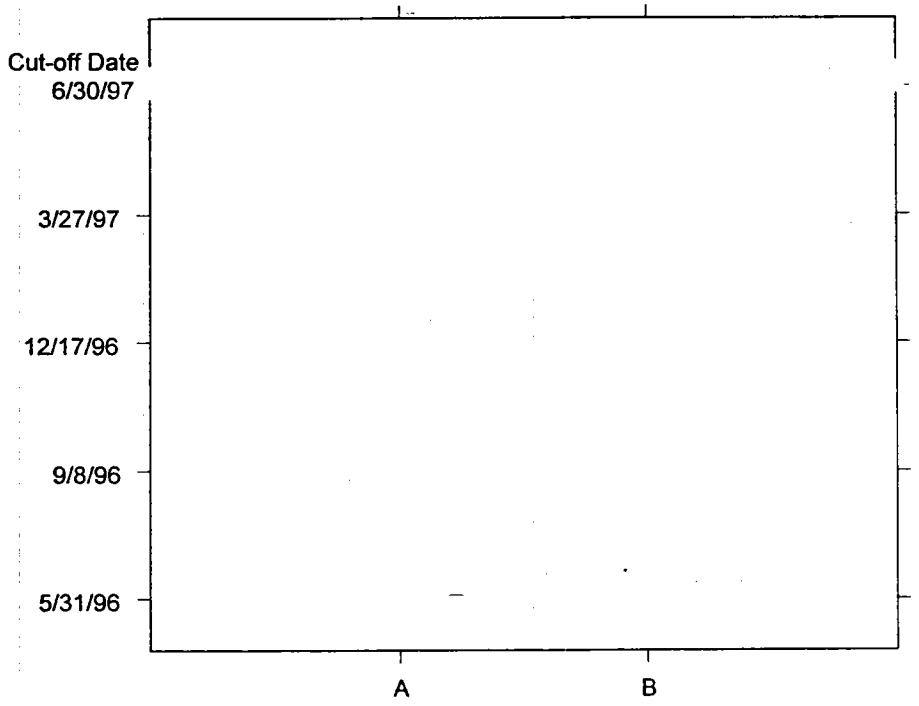
Table 21. FDA Summary Table of Censoring Dates for Survival

Treatment Arm	*Arm A*		*Arm B*	
	N	*%*	*N*	*%*
Number of Patients	*189*	*100*	*90*	*100*
Dead by cut-off date (6/30/97)	***123***	***65***	***71***	***79***
Censored	***66***	***35***	***19***	***21***
• *Before 6/30/97*	*26*	*14*	*9*	*10*
• *On 6/30/97*	*40*	*21*	*10*	*11*
- *last ff-up on 6/30/97*	*7*	*4*	*1*	*1*
- *last ff-up after 6/30/97*	*33*	*17*	*9*	*10*

Twenty-six patients (14%) in Arm A were alive but censored before the cut-off date. Five of the 26 patients were lost to follow-up between 6/3/96 and 5/15/97. Forty patients (21%) in Arm A were censored at the cut-off date; however, 33 of the 40 patients (17%) were known to be alive for up to 1 ½ months after the censor date.

The following box and whisker graph shows a tight interquartile range (shaded areas) of approximately one week from the cut-off date for patients in Arm A, compared to approximately 6 weeks for patients in Arm B. This suggests more rigorous follow-up of patients in Arm A towards the cut-off date compared to a corresponding proportion of patients in Arm B. The five in each arm were those who were lost to follow-up.

Figure 3. Box and Whisker Plot for Censoring

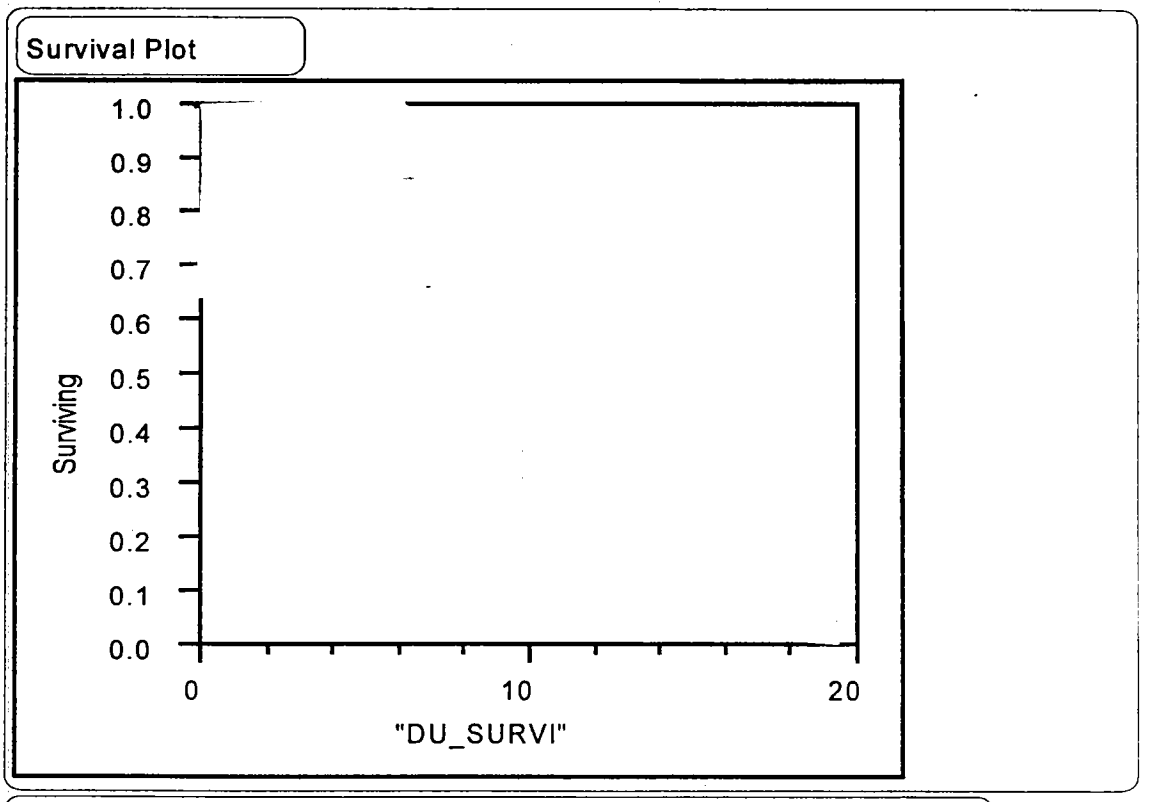


Arm A= CPT-11+BSC (N=66) **Arm B= BSC (N=19)**

Overall, the assignment of censor dates may have placed patients in Arm A at a disadvantage compared to Arm B since there were numerically more patients who were alive and censored earlier than the cut-off date and more patients who were alive after the cut-off date in this arm.

The Kaplan-Meier for survival curve created from "JMP" below confirms the sponsor's report that the probability of being alive when treated with CPT-11 and BSC is constantly and significantly superior compared to BSC alone (p=0.0001).

Figure 4. Kaplan-Meier Survival Curves,
(A= CPT-11 +BSC Arm; B=BSC Arm)



Tests Between Groups

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	14.5772	1	0.0001
Wilcoxon	14.1694	1	0.0002

The FDA's and the sponsor's survival analyses agree:

Table 22. Sponsor vs. FDA Reviewer's Survival Analysis

	SPONSOR		*FDA*	
	Arm A (N=127)	Arm B (N=129)	*Arm A (N=127)*	*Arm B (N=129)*
Cut-off/Censor Date	6/30/97		*6/30/97*	
Median Survival (months)	9.2	6.5	*9.2*	*6.18*
Range				
p-value (log-rank)	0.0001		*0.0001*	

The median survival is reached at 9.2 months in Arm A and 6.5 months in Arm B. According to the sponsor, the likelihood of being alive at 6, 9, and 12 months is increased by 1.33, 1.8 and 2.62 respectively when treated with CPT-11 +BSC compared to BSC alone.

Reviewer's comment: *As noted in Table 19, the median time from diagnosis to randomization of patients in Arm A was similar (19.3 months) to patients in Arm B (17 months). Median survival was calculated from the time of diagnosis of colorectal cancer. An unadjusted analysis also showed a significant difference in survival in favor of patients in Arm A (p=0.008) with a median survival of 33.8 months (28.682, 36.567) and 26.6 months for Arm B (21.585, 31.573).*

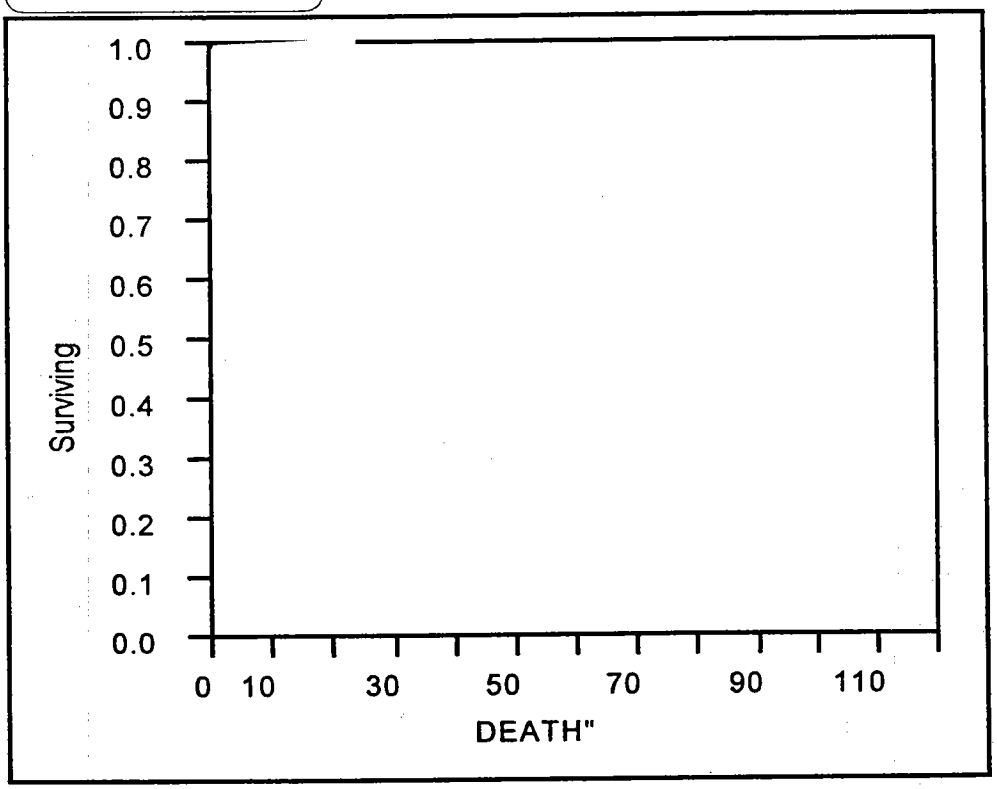
Figure 5. FDA Analysis of Survival from Date of Diagnosis (A=CPT-11 +BSC; B= BSC)

Product-Limit Survival Estimates

Time Variable: DEATH"

Censoring Variable: "MONTHS
"

Survival Plot



Tests Between Groups

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	7.1114	1	0.0077
Wilcoxon	4.6677	1	0.0307

Reviewer's comment: *Compared to Arm B, more patients in Arm A received other therapies after being taken off CPT-11. These include systemic chemotherapy, local radiation and surgery.*

Table 23. FDA Analysis of Subsequent Therapy

Treatment Arm	*Arm A*		*Arm B*	
	N	*%*	*N*	*%*
Number of Patients	*189*	*100*	*90*	*100*
Chemotherapy	*40*	*21*	*5*	*6*
- 5-FU ± other chemotherapy	*31*		*3*	
- Others (including 5-FU analogs)	*20*		*--*	
			2	
Radiation	*16*	*8*	*1*	*1*
Surgery	*1*	*0.5*	*--*	*--*
TOTAL	*57*	*30*	*6*	*7*

A test of proportions showed a statistically significant difference favoring Arm A in the number of patients receiving any subsequent therapy ($p<0.0001$, 30% vs. 7%) between treatment arms. There was also a significant difference in the number of patients receiving chemotherapy alone ($p<0.0001$, 21%vs. 6%).

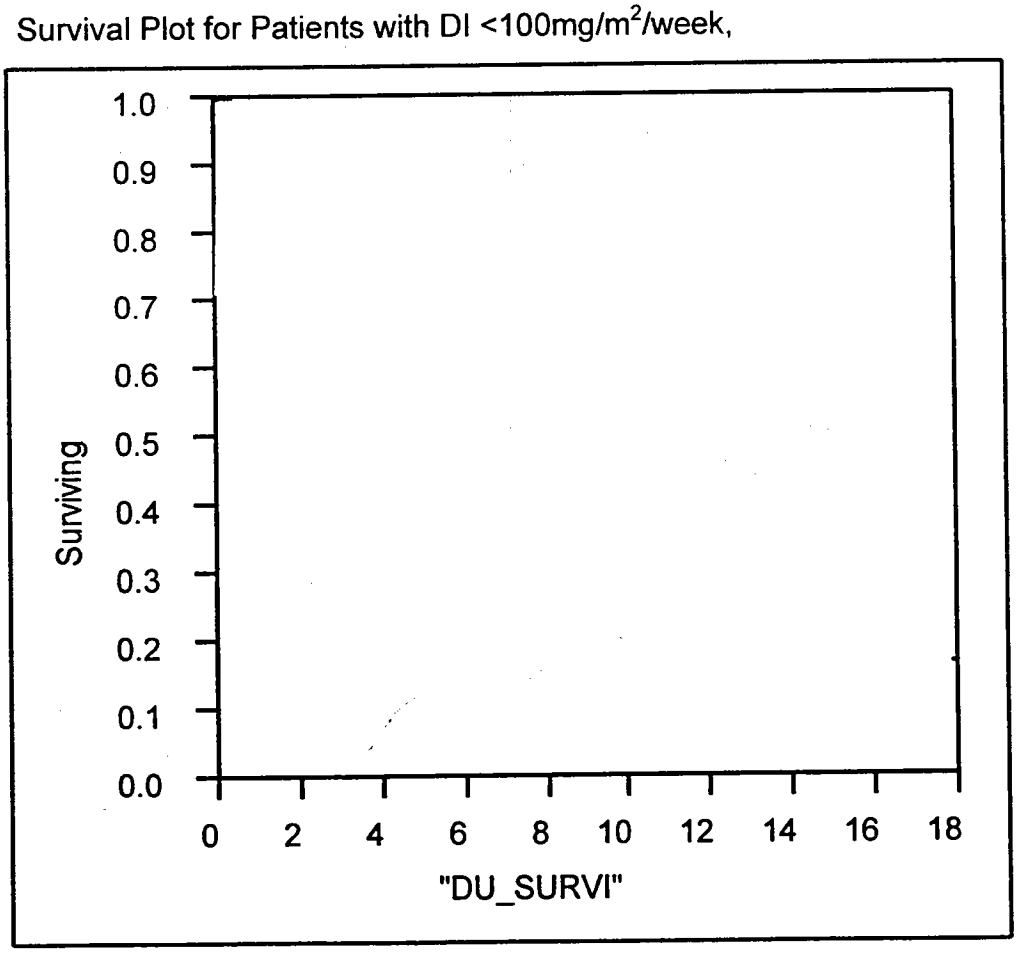
The median survival of patients in Arm A who received subsequent therapies was 11.7 months ($n=32$). The contribution of subsequent therapy to the significant prolongation of overall survival in this group could be debated. All patients who entered the study have refractory disease and those who received subsequent therapies are a minority.

Cox Regression Analysis of Survival : There was a difference between the sponsor and the FDA reviewer's classification of variables considered in the Cox models. It appeared that the sponsor's analysis was based on equal distribution of patients across selected number of intervals. The medical and statistical reviewer performed an exploratory analysis of the variables using subdivisions, which were determined, as possibly having clinical and prognostic relevance. From this analysis, the variables which showed statistically significant differences in survival were Performance Status (0 or 1 vs. 2), Liver Metastases (present vs. absent) and Tumor Location (right vs. left). Please see the FDA Statistical Review by Dr. David Smith for a detailed review.

Reviewer's comment: *In the original NDA submission, patients enrolled in the studies were treated with doses ranging from mg/m^2/week of CPT-11. There seemed to be a dose response relationship in that more patients treated with 150 mg/m^2 responded. In studies the dose of CPT-11 were lowered to 300 mg/m^2 for patients who experienced dose limiting toxicity and in certain groups of patients such as the elderly and those with PS of 2. An exploratory analysis of the survival of patients who received a dose intensity of ≤100 mg/m^2/week (assuming a dose of 300 mg/m^2/3-week cycle) was done to confirm this correlation.*

For study 33 of the 189 patients (17%) treated with CPT-11 received a total dose intensity less than 100 mg/m^2/week. The median survival was 10.12 months (range months). Compared to the total population in Arm A, (median survival 9.2 months), adjustment of CPT-11 dose for toxicity and for certain patient groups at the start of treatment probably was not associated with a worse survival.

Figure 6. FDA Analysis: Survival Plot for Patients with Dose Intensity of CPT-11 <100 mg/m2/week



Clinical Benefit

The major weakness of the Clinical Benefit analysis is the retrospective evaluation of data. The sponsor defined the following time to event endpoints: (1) pain-free survival, (2) symptom free survival, (3) survival without performance status deterioration, and (4) survival without >5% weight loss.

Table 24. Sponsor's Evaluation of Clinical Benefit Endpoints

	Arm A	Arm B	p-value
Pain-free Survival			
No pain at baseline	83	33	
Events	61 (73%)	26 (79%)	
Censored	22 (27%)	7 (21)	
Median duration (months)	6.9	2.0	**0.003**
Range (months)			
Symptom-fee Survival			
No symptoms at baseline	59	19	
Events	49 (83%)	15 (79%)	
Censored	10 (17%)	4 (21%)	
Median duration (months)	5.9	4.1	0.2
Range (months)			
Survival w/o PS Deterioration			
Baseline	189	90	
Events	132 (70%)	71 (79%)	
Censored	57 (30%)	19 (21%)	
Median duration (months)	5.7	3.3	**0.0001**
Range (months)			
Survival without Weight Loss			
Baseline	189	90	
Events	122 (65%)	53 (59%)	
Censored	67 (35%)	37 (41%)	
Median duration (months)	6.4	4.2	**0.018**
Range (months)			

***Reviewer's comment**: The terminology for the above clinical benefit endpoints are probably more appropriately termed as: "Time to Pain Onset", "Time to Onset of Symptoms", "Time to Performance Status Deterioration" and "Time to ≥5% Weight Loss".*

Reviewer's comment: Pain-Free Survival (Time to Pain Onset)
Only a small proportion of patients in either arm were pain-free at baseline: only 44% (83/189) in Arm A and 37% (33/90) of patients in Arm B. Because of the retrospective nature of data collection, the completeness of data collection and the relation of pain to the tumor are questionable. The sponsor states that analgesic consumption was constantly higher in Arm B compared to Arm A; however, patient follow-up was not at equal intervals between the treatment arms and the data was collected retrospectively. Therefore, the robustness of this analysis is questionable.

Reviewer's comment: Symptom-free Survival (Time to Onset of Symptoms)
The sponsor retrospectively identified symptoms that are likely to be related to tumor. However, the submission stated that "this analysis made no sense due to poor reporting in the CRF by investigators who obviously encountered difficulties to report symptoms which could be both tumor related and drug related". I agree.

***Reviewer's comment: Survival without PS Deterioration (Time to Performance Status Deterioration)** Performance status was prospectively evaluated by investigators during interval visits. According to the sponsor's report, 33% of patients in Arm A with a PS of 1 or 2 at baseline were able to improve their PS compared to patients in Arm B ($p=0.002$). Thus, they were able to show not only a statistically significant difference in deterioration but also an improvement for patients in Arm A. These results are consistent with the Cox regression analysis of covariates for survival and may truly represent a clinical benefit.*

Reviewer's comment: Survival without Weight Loss (Time to ≥5% Weight Loss)
Change in weight may or may not be a true indication of clinical benefit. For example, unwanted weight gain from ascites and/or edema is very common among these patients. On the other hand, other factors such as overzealous diuresis, dehydration from nausea, vomiting or diarrhea, and poor hydration may be responsible for weight loss. Review of concurrent medications showed that at least 75 patients (27%) used diuretics for the management of edema, ascites, etc..

Quality of Life:

Analyses of fifteen scales by multivariate analysis of variance, taking into account change from baseline was significant ($p<0.001$). The univariate analyses showed significant advantages in favor of CPT-11 for cognitive functioning, global health status and the following symptoms: pain, dyspnea, appetite loss, constipation and financial impact. Diarrhea was in favor of BSC ($p=0.008$).

The 15 scales of the quality of life instrument QLQ-C30, were subdivided into: (1) Five Functional Scales : **physical functioning**, role functioning, emotional functioning, cognitive functioning, social functioning; (2) **Global Health Status**; and (3) Nine Symptom Scales: **fatigue, nausea/vomiting, pain**, dyspnea, sleep disturbance**, appetite loss, constipation, diarrhea** and financial impact.

> ***Reviewer's comment***: *There was no prospective plan for controlling Type I error to account for the number of QOL subscales that were considered, some of which may have more clinical relevance than the others(in bold font).*

A multivariate analysis of variance was performed to compare the 15 scales globally from baseline. Univariate analyses of baseline was also performed on each subscale. A repeated measures analysis defined three week windows to compare parameters with the same time scale. Missing values were considered as random factors.

> ***Reviewer's comment***: *QOL testing was done at baseline, Week 3, 6, then every 6 weeks. Patient compliance was good (approximately 80%) up to 12 weeks of testing. However, correlation across repeatedly measured endpoints is still a concern.*
>
> *The FDA Statistical review (Dr. D. Smith) applied longitudinal analyses methods by using the generalized estimating equation (GEE) approach to cope with informative correlation among observations per subject. It was found that estimated linear trends for four out of six subscales were different for those subjects who dropped out on or before the third course (labeled as "Dropouts") and those who dropped out after the third course (labeled as "Completers"). It was concluded that the pattern could not be ignored.*

A general linear model for each subscale using treatment arm, time, and treatment time as explanatory variables was used. For response variables, the sponsor considered the following: raw scores, difference from baseline, worst score, change from baseline of worst score, and scores with 0 (imputed) for patients who died. The following table from Dr. Smith's review summarizes results from QOL subscales with significant differences in the sponsor's analysis:

Table 25. QOL Subscales with Significant Results

Change from Baseline	**p-value (favored arm)**	**Worst Score**	**p-value (favored arm)**
Cognitive Function	<0.001 (A)	Physical Function	<0.001 (A)
Global Health	0.003 (A)	Role Functioning	0.002 (A)
Pain	0.008 (A)	Cognitive Function	0.006 (A)
Dyspnea	0.035 (A)	Social Function	0.009 (A)
Appetite Loss	<0.001 (A)	Fatigue	0.006 (A)
Financial Impact	<0.001 (A)	Pain	0.001 (A)
Diarrhea	0.017 (B)	Dyspnea	0.029 (A)
		Appetite Loss	<0.001 (A)
		Constipation	0.004 (A)
		Diarrhea	<0.001 (B)

The FDA statistical reviewer analyzed three subscales identified among the list of clinically relevant subscales with the following results:

Table 26. FDA Statistical Reviewer QOL Results

	p-value (favored arm)	
	Dropouts	Completers
Physical Functioning	0.58	0.38
Pain	0.3I (B)	0.28
Nausea/Vomiting	0.87	0.005 (B)

***Reviewer's comment**: The disparity in results between the sponsor and the FDA obviously resulted from differences in methodology of analyses used. Additional analyses of other clinically relevant subscales will be done by the FDA reviewers in order to achieve a consensus regarding quality of life which can have an impact on labeling and marketing of CPT-11 if approved.*

Safety

A descriptive analysis of adverse events was performed on the randomized population for both treatment arms according to the NCI Common Toxicity Criteria.

The following table shows the frequency of **Grade 3 and 4** adverse events in the study as reported by the sponsor (rounded to the nearest whole number). Except for hematologic toxicities, only Grade 3+4 toxicities with an incidence of >5% are shown; and those with a significant difference between the treatment arms are in bold font.

Table 27. Sponsor's Summary of Grade 3 and 4 Toxicity

	ARM A (N=189) (N/%)			ARM B (N=90) (N/%)		
	Gr 3	Gr 4	Gr3/4	Gr3	Gr4	Gr3/4
Anemia	11 (6)	3 (2)	14 (7)	5(6)	1(1)	6(7)
Leukopenia/neutropenia	**22(12)**	**20(11)**	**42(22)**			
Thrombocytopenia	1 (.5)	1 (.5)	2 (1)			
Fever + neutropenia	2 (1)	2 (1)	4 (2)			
Neutropenia + Infection	1 (.5)	1 (.5)	2 (1)			
Nausea	**26(14)**	--	**26(14)**	3 (3)		
Vomiting	**20(11)**	**6(3)**	**26(14)**	6(7)	1(1)	7(8)
Diarrhea	**27(14)**	**14(7)**	**41(22)**	2(2)	3(3)	5(6)
Constipation	14(7)	4(2)	18(10)	3(3)	4(4)	7(8)
Cholinergic symptoms	**21(11)**	**2(1)**	**23(12)**			
Asthenia	28(15)	--	28(15)	15(17)	2(2)	17(19)
Neurologic symptoms	23(12)	--	23(12)	11(12)	1(1)	12(13)
Pain	33(17)	2(1)	35(18)	19(21)	1(1)	20(22)
Abdominal pain	24(13)	2(1)	26(14)	14(16)		14(16)
Infection w/o neutropenia	14(7)	2(1)	16(8)	3(3)	--	3(3)
Cardiovascular disorders	9(5)	7(4)	16(8)	2(2)	1(1)	3(3)
Liver	13(7)	3(2)	16(8)	4(4)	2(2)	6(7)
Lung	14(7)	5(3)	19(10)	5(6)	2(2)	7(8)
Other	38(20)	22(12)	60(32)	14(16)	11(12)	25(28)

(Final Study Report, p.71)

Reviewer's comment: *The incidence of grade 3 and 4 neutropenia and non-hematologic toxicities such as nausea, vomiting, diarrhea and cholinergic*

symptoms (bold face) was significantly greater on the CPT-11 arms but were expected.

Reviewer's comment: *Cholinergic symptoms seem to be more prevalent in patients treated with 350 mg/m^2 of CPT-11 every three weeks compared to the weekly schedule. The proposed package insert contains more information describing the frequency, severity and treatment of these symptoms based on experience from a Phase I study, M6475/0024.*

Reviewer's comment: *There were earlier but rare reports of idiosyncratic pulmonary toxicity especially on patients with pulmonary tumors that may be related to treatment with CPT-11. Adverse events described as "Lung" need to be clarified.*

Reviewer's comment: *The following table compares the most common Grade 3 and 4 adverse events of two dosing schedules of CPT-11. Data on the weekly schedule was obtained from the current package insert. The higher incidence of severe late diarrhea may be related to the weekly schedule but may also be due to the inadequacy of loperamide treatment in the earlier clinical trials of CPT-11.*

	% Patients with Grade 3 and 4 Toxicity	
	Q3 weeks[a] (N=189)	Weekly x4 [b] (N=304)
Leukopenia/neutropenia	22	28
Nausea	14	17
Vomiting	14	12
Diarrhea	22	31
Cholinergic symptoms	12	8[c]

[a] patients treated with CPT-11, 325 mg/m^2 every 3 weeks in study

[b] patients treated with CPT-11, 125 mg/m^2 weekly x4 every 6 weeks enrolled in Studies 001, 003 and 006

[c] Identified as "Early diarrhea"

Death within 30 Days of Treatment (Arm A)

A total of eight patients died within 30 days of last treatment with CPT-11. The following table compares the assessment by the sponsor and the FDA of the relationship of study treatment to death:

Table 28. Comparison of Sponsor and FDA Review of Deaths within 30 Days of Last Treatment

PATIENT ID	CAUSE OF DEATH	RELATIONSHIP TO TREATMENT	
		SPONSOR	*FDA*
	Sepsis, neutropenia, mucositis diarrhea (C1D10)	Probable	*Definite*
	Diarrhea, asthenia, weakness (C2D9)	Possible	*Probable*
	Cardiac Insufficiency (autopsy)	Not related	*Not related*
	Fever, diarrhea then upper GI bleed, vomiting with aspiration on (C1D17) (autopsy: hemorrhagic gastritis, coronary insufficiency)	Not related	*Probable*
	Pain, weakness, confusion before death, w/ history of neutropenic sepsis during the cycle (C3D18)	Not related	*Possible*
	Post-op abdominal pain, hypotension, shock (C2D7)	Not related	*Not related*
	Unknown (C2D9)	Unknown	*Unknown*
	Disease Progression (C3D21)	Not related	*Not related*
	Not Related Possible Probable Definite Unknown	5 0 1 0 1	*3* *1* *2* *1* *1*

There were 8 of 189 (4%) deaths within 30 days of CPT-11. The FDA reviewer's impression was four (2%) patient deaths were possibly to definitely related to treatment compared to one patient (0.5%) by the sponsor's analysis.

Hospitalizations

According to the sponsor's review of hospitalization data:

Table 29. Hospitalizations due to Adverse Events

Patients with	Arm A (N=189) (N/%)	Arm B (N=90) (N/%)
At least one hospitalization due to serious adverse events	136 (72)	57 (63)
Number of Hospitalizations per Patient Median Range	2.0	1.0
Number of Days in Hospital Median Range	15.0	11.0

(summarized from addendum submission, July 27, 1998; volume 23.1)

***Reviewer's comment**: Additional information was requested from the sponsor regarding hospitalizations in this study including individual patient data listings and transcribed copies of the Clinical Experience Forms which the investigators were required to fill out.*

In cases where there were multiple reasons for hospitalization, the adverse event with the highest toxicity grade was considered as the reason for hospitalization. The duration of hospitalization could not be determined in most cases since at the time of reporting by the investigators, the patients were usually still in the hospital.

Table 30. FDA Analysis of Hospitalizations

Reason for Hospitalization	*Arm A*	*Arm B*
Diarrhea	*44*	*3*
Fever, No Infection, No Neutropenia	*31*	*3*
Fever + Neutropenia	*13*	*0*
Nausea/Vomiting	*30*	*6*
Pain	*26*	*15*
Neurocortical	*18*	*6*
Anemia	*16*	*2*
Liver	*11*	*7*
Others	*79*	*42*
TOTAL	**268**	**85**

A total of 1154 courses of CPT-11 were given to 189 patients in Arm A, of which, 268 courses (23%) were associated with hospitalizations. The most common reasons for hospitalization among patients in Arm A were diarrhea, fever, nausea and vomiting, and pain. There were 13 courses (1%) associated with fever/neutropenia. There were 85 episodes of hospitalization in Arm B, for which pain was the most common reason. For patients receiving CPT-11, 23% of the treatment courses were associated with hospitalizations mostly due to adverse events from treatment.

Figure 7. FDA Reviewer's Summary of Benefits, Risks and Concerns, Study

BENEFITS/ STRENGTHS	RISKS/ WEAKNESSES	CONCERNS/ UNCERTAINTIES
Study Design and Conduct		
• Large, randomized, well-controlled • Independent monitoring committee • BSC control arm • Well-balanced patient population with mostly resistant/refractory colorectal cancer	• Unequal frequency of patient follow-up between treatment arms	
Efficacy		
• Well-controlled and appropriate censoring • Statistically significant median survival advantage (from date of randomization) favoring CPT-11 • Statistically significant median survival (from date of diagnosis) favoring CPT-11 • Lower dose intensity (<100 $mg/m^2/wk$) with no detrimental effect on survival		• Positive survival impact of subsequent chemotherapy received by more patients in CPT-11 arm • Uncertain survival correlation between weekly (approved) schedule and the every three week schedule
Clinical Benefit		
• Prospective collection of PS data, time to PS deterioration favoring the CPT-11 arm	• Retrospective analysis of pain-free survival, symptom-free survival, and survival without weight loss	

BENEFITS/ STRENGTHS	RISKS/ WEAKNESSES	CONCERNS/ UNCERTAINTIES
Quality of Life		
• Good patient compliance • Significant advantage favoring CPT-11 as regards cognitive function, global health, pain, dyspnea, appetite loss and financial impact per sponsor's comparison from baseline scores • Significant advantage favoring CPT-11 as regards physical functioning, role functioning, cognitive functioning, social function, fatigue, pain, dyspnea, appetite loss and constipation per sponsor's comparison of worst scores	• Retrospective analysis • No prospective plan for controlling Type I error to account for multiple subscales • Sponsor's analysis assumed random occurrence of missing data • Significant advantage favoring the BSC arm as regards diarrhea per sponsor's comparison to baseline and worst scores	• FDA Statistical review results using longitudinal analysis methods separating "dropouts" from "completers" different from sponsor's results • Analyses of other clinically relevant subscales using the FDA method need to be done
Safety		
• Toxicity profile probably similar to weekly dosing schedule approved in the U.S. • Low on-study death rate (2% by FDA, 0.5% by sponsor) • Safety profile well-described in supporting phase I trials	• Unequal frequency of monitoring • On-study lab results not available for verification • Greater incidence of leucopenia, neutropenia, nausea, vomiting, diarrhea and cholinergic symptoms • More hospitalizations mostly due to treatment adverse events	

Study

This is a non-blinded, parallel randomized, multicenter phase III study comparing CPT-11 to another best estimated chemotherapy regimen in patients with metastatic colorectal cancer after failure of treatment with 5-FU.

***Reviewer's comment**: The following section was modified from the final version of the protocol text. Important amendments and are highlighted in the protocol and summarized in a separate section .*

Title:

A Randomized Phase III Multicenter Trial Comparing Irinotecan Hydrochloride Trihydrate As Single Agent to Best Estimated Chemotherapy Regimen in Patients with Metastatic Colorectal Cancer After Failure of 5-Fluorouracil Containing Regimen

Principal Investigator:

P.H. Rougier, MD
Hopital Ambroise Pare
Boulogne, France

Study Centers

46 centers in the following countries: France: 4, Belgium: 7, The Netherlands: 3, Germany: 9, Sweden: 1, Italy:7, Spain:5, Austria:2, Greece:4, Switzerland: 3, Portugal:1 (12/5/95: 50 centers)

Study Period : September 29, 1995 to July 14, 1997

Amendment 1: 12/5/95
Amendment 2: 8/8/96
Amendment 3: 3/13/97

***Reviewer's comment**: The above amendment dates are designated as A1, A2, and A3 throughout the protocol text.*

Summary of Amendments (Complete List):

12/5/95 (A1)

- to clarify the inclusion criteria regarding the number of prior regimens accepted before study entry
- to modify the following inclusion criteria: (1) to exclude patients with prior treatment with ralitrexed or oxaliplatin; (2) to exclude patients with prior or current history of curatively treated cancers, other than colorectal cancer, non-melanoma skin cancer or in situ carcinoma of the cervix; (3) to specify which kind of abdominal masses were excluded
- to correct unclear descriptions of the comparative arm (Arm B)
- to homogenize follow-up schedules for adverse events, quality of life and socio-economic assessments
- to modify the study coordination, with became the sponsor instead of the EORTC-GI group, and to introduce the EORTC-GI group as the responsible body for the quality control of the study
- to switch the inclusion location from Brussels, Belgium to in Paris, France
- to update the list of criteria to be checked for patient registration
- to update the list of participating countries and investigators
- correction of typographical errors

8/8/96 (A2)

- to recommend dose reduction of CPT-11 in case of severe diarrhea
- to update the list of investigators
- modify the name of the Clinical Project Leader

3/13/97 (A3)

- The need for a prolongation of the cut-off date since the required number of events was not reached at the predetermined cut-off date in March, 1997. The 177th death occurred on July 14, 1997, which became the official cut-off date after which the survival analysis was performed.

Reviewer's comment: Electronic data submitted for survival analysis was not updated for the July 14, 1997 cut-off date. The basis of the FDA survival analysis was the earlier cut-off date of March 5, 1996.

Objectives

Primary:

To compare the **survival** after treatment with CPT-11 plus best estimated 5-FU based chemotherapy regimen in patients with metastatic colorectal cancer who have previously failed a 5-FU containing regimen.

Secondary:

To compare the **median time to progression, response rate, median time to disease related symptoms, quality of life and other clinical benefit parameters, toxicity/symptomatology.**

Inclusion Criteria

- Histologically or cytologically proven adenocarcinoma of the colon or rectum
- Progressive metastatic disease at entry defined as:

  (1) Proof of progression determined by two imaging studies separated by less than 6 months;

  (2) Increased CEA: e.g., progressive increase of at least 50% on 2 consecutive CEA values with at least one month interval between each sample. A third confirmatory CEA value which should be equal or greater than the second should validate the 50% increase.

  ***Reviewer's comment**: Progression by increase in CEA was more stringent in study*

  Bi- or unidimensionally measurable or non-measurable disease provided that the CEA is increased (e.g., absolute value of >10 ng/ml) If only one lesion is present, histology or cytology confirmation of disease is mandatory.

- Time between last antitumor treatment and randomization must be at least 4 weeks for chemotherapy (6 weeks for nitrosoureas and mitomycin C) and 4 weeks for radiation therapy unless the area involved <20% of bone marrow areas in which case the patient may start study treatment earlier
- Patients must have either a clear documented progression while receiving an adequate 5-FU containing regimen as their last treatment or within three months after the last 5-FU infusion of their last 5-FU containing regimen. The intent of this 5-FU regimen could be adjuvant or palliative.
- The overall number of prior chemotherapy regimens must not exceed two if one of them was given as adjuvant and must not exceed one if only palliative regimens were given. (Prior to A1: overall number of prior chemotherapy not exceeding 3

if one was given as adjuvant, and not exceeding 2 if only palliative regimens were given.)

Reviewer comment: *Patients who were taken off prior 5-FU treatment for reasons other than disease progression may be more sensitive to 5-FU. In addition, patients were allowed less prior chemotherapy compared to the patients*

- 18-75 years old
- WHO Performance status ≤ 2 i.e., up and about more than 50% of waking hours, or less 50% of waking hours in bed or armchair
- Written informed consent
- Adequate hematological, renal and hepatic functions
    (1) ANC ≥2.0 x 10^9/l platelets ≥ 100x10^9
    (2) total serum bilirubin≤ 1.25 x upper normal limits
    (3) creatinine ≤ 135 mmol/l (2 mg/dl)
    (4) AST and ALT ≤3x upper normal limits. In case of liver metastasis, bilirubin ≤1.5x upper normal limits and AST and ALT ≤5x upper normal limits
- Able to comply with scheduled follow-up

Exclusion Criteria

- Pregnant or lactating patients, or those not implementing adequate contraceptive measures during study
- More than one regimen of palliative chemotherapy for advanced and/or metastatic disease
- Previous treatment with topoisomerase I inhibitors, oxaliplatinum or raltitrexed (A1)
- Bulky disease defined as more than 50% of liver involvement or more than 25% lung involvement or abdominal mass (excluding hepatic tumors) ≥10 cm (Prior to A1: palpable abdominal mass)
- Presence or history of CNS metastases
- Unresolved bowel obstruction or subobstruction/diarrhea
- Chronic diarrhea

- Other serious illness or medical condition such as unstable cardiac disease requiring treatment, history of significant neurologic or psychiatric disorders, active uncontrolled infection, and other underlying medical conditions that would impair the ability of the patient to participate in the study
- Any contraindication for the best estimated chemotherapy chosen
- Past or current history of neoplasm other than colorectal carcinoma, except for curatively treated non melanoma skin cancer or in situ carcinoma of the cervix
- Concurrent treatment with any other experimental drugs or within a clinical trial (starting one week prior to randomization)
- Concurrent treatment with any other anti-cancer therapy (at baseline or within 28 days prior to study entry or 35 days in case of mitomycin C or nitrosoureas)
- Patients clearly intending to withdraw from the study if they are not randomized to Arm A (CPT-11)

Work-up

Table 31. Baseline Investigations, Study

INVESTIGATIONS	TIMING
History/P.E.	≤ 48 hours prior to randomization
Hematology (CBC, PT/PTT) Biochemistry (alk phos, LDH, AST, ALT, creatinine, protein)	≤ 48 days of randomization
Tumor Measurements (CEA, CT scans)	≤14 days prior to randomization
Quality of Life	Within one week after randomization but prior to first treatment infusion
Other Investigations	As clinically indicated

Table 32. On Study Investigations, Study

INVESTIGATIONS	TIMING
History/P.E.	Before infusion q 3-5 wks, Q 6-8 weeks off treatment (Prior to A1: Every 6 weeks off treatment)
Concomitant Tharapy	Before infusion q 3-5 wks, Q 6-8 weeks off treatment (Prior to A1: Every 6 weeks off treatment)
Hematology (CBC, PT/PTT)	Wkly before infusion, As indicated off treatment
Biochemistry (alk phos, LDH, AST, ALT, creatinine, protein)	Q 3-5 wks, As indicated off treatment
Tumor Measurements: CT scans ± CEA	Q 9-12 weeks
Adverse Events	Before infusion q 3-5 wks, Q 6-8 weeks off treatment (Prior to A1: Every 6 weeks off treatment)
Quality of Life	At baseline, 2nd and every 2 visits, then q 6-8 weeks off treatment (Prior to A1: QOL at baseline, visit 1 and 2, then every 2 visits up to one year)
Socio-economic data	Every visit on treatment, then ever 6-8 weeks off treatment (Prior to A1:Every visit)

***Reviewer's comment**: The frequency of follow-up is not equal between treatment arms and within different treatment subgroups in Arm B.*

Study Treatment

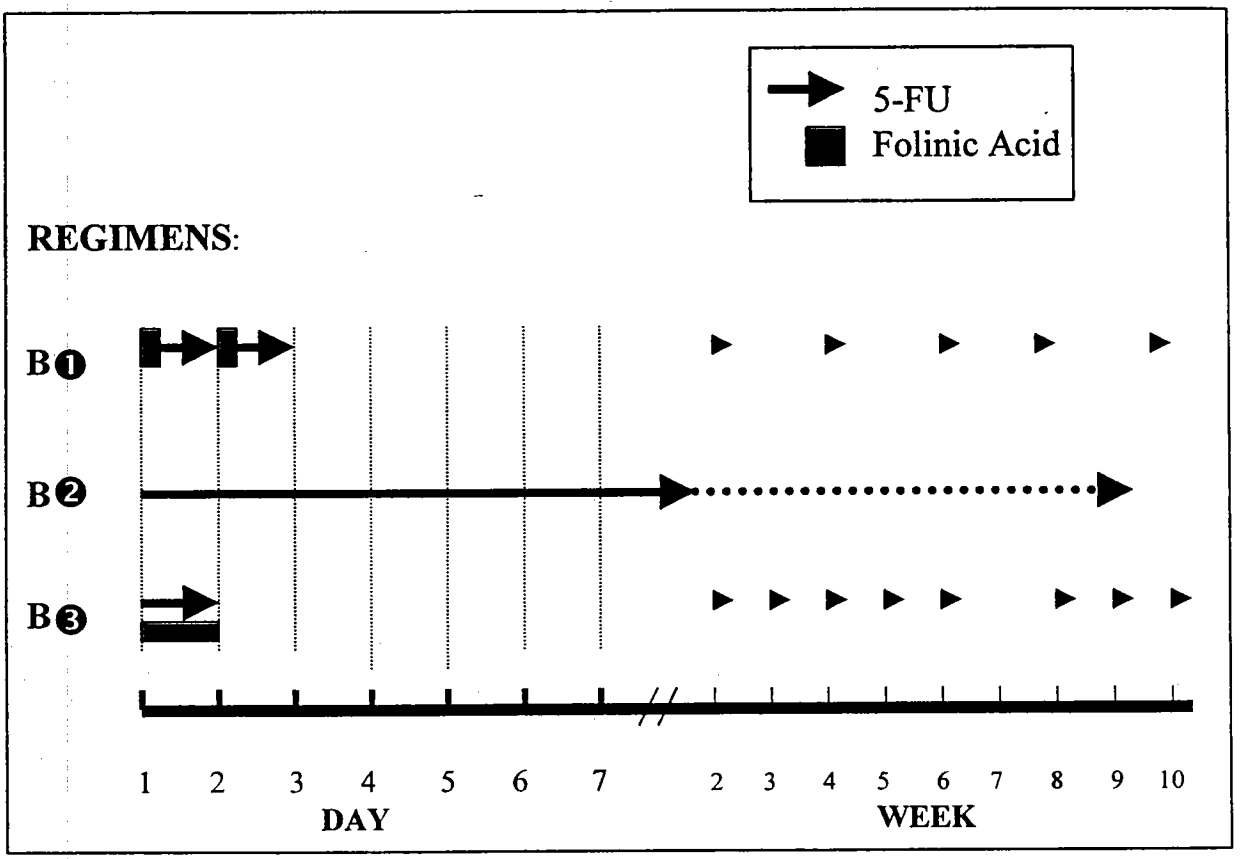
Arm A: CPT-11, 350 mg/m^2 as a 90-minute intravenous infusion on day 1 every three weeks

- Treatment with CPT-11 within one week of randomization.
- The starting dose for patients aged ≥ 70 years or performance status =2 should be reduced to 300 mg/m^2.
- Chemoembolization in patients with progressive liver metastases is allowed

Arm B: Best Estimated 5-FU Based Chemotherapy Regimen (B5-FU)

Patients enrolled in this arm received one of the following three chemotherapy regimens:

Figure 8. FDASchema for Alternative 5-FU Treatment Regimens
Arm B



B❶ Folinic Acid, 200 mg/m^2, iv over 2 hours
followed by 5-FU 400 mg/m^2 iv bolus
followed by 5-FU, 600 mg/m^2, continuous iv infusion over 22 hours
on Days 1 and 2 every two weeks (Prior to A1: on two consecutive days)

B❷ 5-FU, 250-300 mg/m^2/day (Prior to A1: 300 mg/m^2/day), protracted continuous iv infusion using a portable infusion pump until toxicity

B❸ 5-FU 2.6-3 g/m^2/day, iv over 24 hours, every week x 6 weeks
with or without folinic acid 20-500 mg/m^2/day every week x 6 weeks
with two weeks rest between two cycles (Prior to A1: no folinic acid)

Background Information of Best Estimated Chemotherapy Regimen

The impact of chemotherapy on the survival of patients with metastatic colorectal cancer who progressed after the first palliative chemotherapy regimen remains controversial. The median survival for such patients is estimated to be 4 to 8 months.

B❶: This schedule has been reported to double the response rate and improve time to disease progression in a large multicenter randomized trial where it was compared to a classical five day schedule of 5-FU associated with low-dose folinic acid.[5]

B❷: 5-FU 300 mg/m^2/day, continuous infusion until progression[6,7] which showed overall response rates of 15% (95% CI: 1-29.4%), N=29; and 33% (95% CI: 11-55%), N=18 respectively. This was confirmed by Findlay et al. In 52 truly resistant out of 124 patients enrolled in the trial with an 18% response rate (95%CI: 9-32%).[8] Another study conducted in Singapore used a lower dose of 5-FU (250 mg/m^2/day) showed an overall response of 46% (12/26 patients) with a median duration of 5 months. Ten patients from this group were previously untreated. [9]

B❸: Known to produce responses or stabilization of disease after treatment with the 5-FU bolus schedule, as shown by Adarlan, et al.[10] in 10 patients with three responses (30%), and confirmed by Jager in 64 patients (25% response rate, 95% CI: 14-36%)[11] and by Weh in 57 patients (9% response rate, 95% CI:2-16%).[12]

Reviewer's comment: *The distribution of patients in v302 are as follows: Arm A (CPT-11) N=127 (50%); Arm B:* **B❶**: 35 (14%); **B❷**: 39 (15%); **B❸**: 55 (22%). *Arm B patients could receive one of three treatments depending on study center preference. Considering the fact that the different 5-FU infusional regimens may have different efficacy and safety profiles, the acceptability of "Arm B" as single, homogenous arm was a concern. However, the study was not designed nor powered for subgroup comparisons. In addition, the treatment subgroups in Arm B reflected community practice.*

Dose Modification

Arm A

Same as dose reduction plan for Study v310

Arm B

For Regimens B❶ and B❸:

Myelosuppression: On retreatment day, if ANC < 1.5 x 10^9/L or platelets < 100 x 10^9/L, delay for one week. If not recovered, delay for another week. If still not recovered after two weeks, terminate treatment unless there is clear benefit for the patient.

- In case of Grade 4 neutropenia, whatever the duration and whether complicated or not with fever/infection or of Grade 3 neutropenia with fever, a 15% dose reduction will be applied for subsequent courses, unless there is a deficit in dipyrimi-dine deshydrogenase (?). In this case, 5-FU will not be restarted.
- If Grade 4 neutropenia recurs after reduction, a second 15% reduction will be applied
- If Grade 4 neutropenia recurs after the second reduction, treatment will be terminated.

For other Grade ≥2 toxicities ongoing except for alopecia and anemia, drug should be held for a maximum of two weeks from the planned date of reinfusion until resolution to ≤ Grade 1, then reinstituted at a 25% dose reduction. Another reduction can be implemented if medically appropriate.

For Regimen B❷:

Treatment will be interrupted when appearance of any Grade 3 or 4 toxicity (except alopecia) and to be restarted with a 15% dose reduction when complete recovery of all toxicity

Concomitant Treatments,

Table 33. Concomitant Treatments, Study

Atropine (Arm A)	• for acute severe cholinergic symptoms including early diarrhea, sweating, hypersalivation, visual disturbances, lacrimaton • not recommended as prophylaxis on first cycle
Loperamide (Arm A)	• no prophylactic treatment • take 2 caps as soon as first liquid stool, 1 cap q 2 hours for at least 12 hours and up to 12 hours after last liquid stool. Oral rehydration
Antiemetics	• prophylaxis recommended, to be chosen by treatment center
Fluoroquinolone	• for diarrhea > 24 hours despite recommended loperamide treatment. Continue oral rehydration
Antibiotics	• antibiotic prophylaxis not recommended routinely after grade 4 neutropenia ± fever but may be given depending on study center
	• not recommended but may be considered

Discontinuation from Study

- Toxicity
- Disease progression

  Patients who develop brain metastases during study may receive CNS radiation and continue treatment, but considered in progression.
- Patient refusal

Further antitumor therapy (except Topoisomerase I inhibitors) may be administered to control disease-related symptoms.

Follow-up after Treatment Discontinuation

For 30 days to document drug related side effects then,
Every 6 to 8 weeks up to one year to document: (Prior to A1: every 6 weeks)

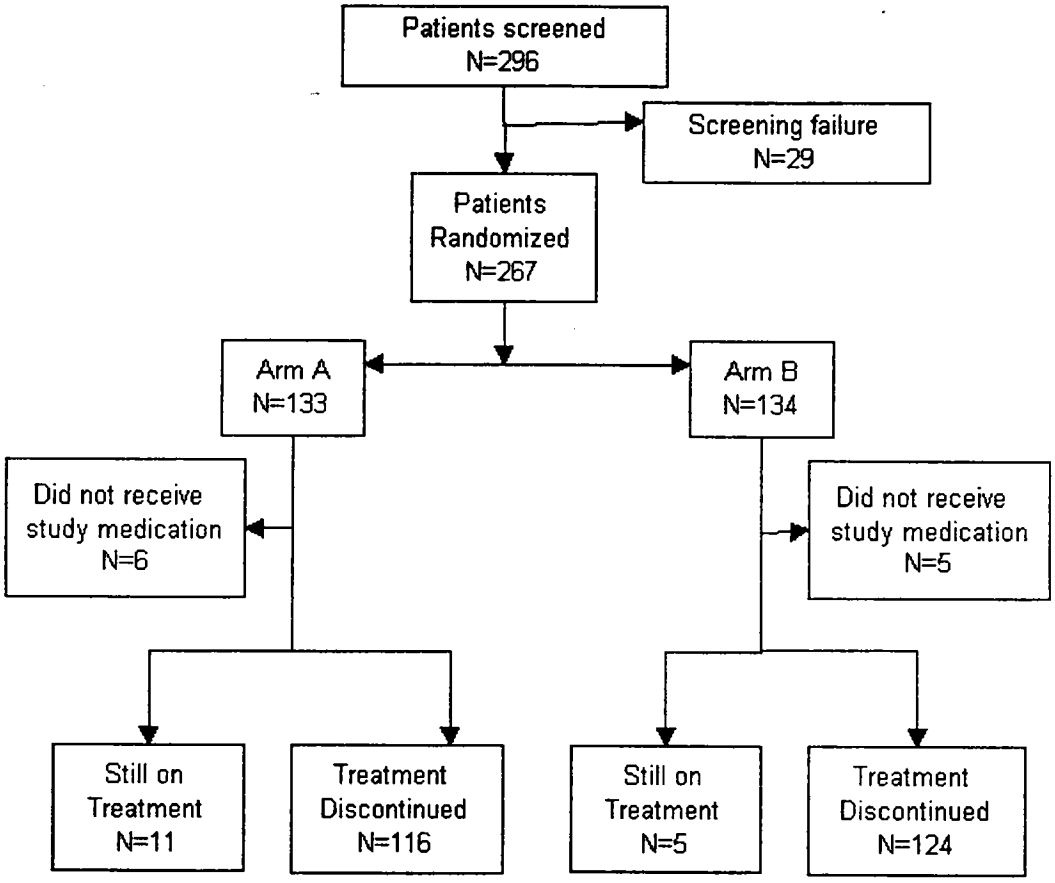
- resolution of side effects
- survival
- disease related signs and symptoms
- quality of life, and
- tumor progression if treatment was stopped before progression

No specific follow-up after one year, but date of death was traced.

Results (Study

Patient Disposition

Figure 9. Disposition of Patients as of March 3, 1997



Patients in each arm fit the statistically required number of patients. There were 127 patients in Arm A and 129 patients in Arm B who represent the intent-to-treat population.

Of the 256 patients enrolled, 15 patients were still on active treatment on the cut-off date. Treatments was discontinued for the following reasons:

Table 34. Reasons for Treatment Discontinuation Study (N=256)

	Arm A (N=127)		Arm B (N=129)	
	No.	%	No.	%
Progressive disease	85	67	102	79
Nonfatal toxicity	13	10	8	6
Consent withdrawn, refused treatment	10	8	9	7
Death due to toxicity			1	0.8
Death due to progressive disease	2	1.6		
Death: Other reasons	1	0.8		
Others	5	3.9	4	3.1

(Final Study Report, vol. 1.40 p.57)

The majority of treatment discontinuation was due to progressive disease. There was one fatal toxicity in Arm B in a patient that experienced severe diarrhea and dehydration. The death of one patient in Arm A for "Other Reasons" was due to acute pulmonary embolism. The most common toxicity causing treatment discontinuation is diarrhea for 10 of the 13 patients in Arm A and 4 of the 9 patients in Arm B.

Randomization Procedure

The accrual goal for was a total of 258 patients. This would show a significant difference in the one-year survival rates of 35% for CPT-11 vs. 20% for the best estimated chemotherapy regimen. A total of 267 patients (133: Arm A and 134: Arm B) were enrolled.

Patients were centrally randomized by Patients were randomly assigned to receive either CPT-11 as a single agent (ArmA) or best estimated chemotherapy regimen (Arm B) with stratification by center and performance status using a minimization procedure.

Table 35. Protocol Deviations

At Randomization	ARM A N=127		ARM B N=129	
Patients	N	%	N	%
Wash-out period not respected	17	13.4	22	17.1
Progressive disease > 3 months after 5-FU	6	4.7	11	8.5
Progression not documented	6	4.7	8	6.2
>1 palliative ± 1 adjuvant 5-FU	2	1.6	0	0
Previous history of other cancer	0	0	1	1
Bulky disease	0	0	1	1
Lab value outside specific range	3	2.4	4	3.1

(summarized from Study Report, p59)

Reviewer's comment: *With regard to time of disease progression after last 5-FU treatment, study was more strict (≤3 months). This resulted in more patients classified as deviations. The exact time to progression required to define patients with resistant disease vary in different studies from 3-12 months; although it could probably be safely assumed that patients who progress earlier have more resistant disease.*

Demographics

Table 36. Pretreatment Characteristics

Treatment Arm	Arm A		Arm B	
	N	%	N	%
Number of Patients	127	100	129	100
Male/Female (%)	72/55	57/43	84/45	65/35
Performance Status (PS)				
0	73	58	69	54
1	44	35	56	43
2	10	8	4	3
PD while on 5-FU	73	58	88	68
PD ≤ 3 months	48	38	29	23
PD ≥ 3 months	6	5	11	8
Intent of Prior Chemo				
Adjuvant only	17	13	19	15
Palliative± Adjuvant	110	87	110	85
Best Response to Prior 5-FU				
CR	4	2	4	5
PR	36	21	20	27
Stable	57	34	24	32
PD	64	38	24	32
Not Evaluable	5	3	2	8
Unknown	3	2	1	1
Median time from diagnosis to randomization (months)	15.7		15.4	
Median time from progression to randomization (months)	0.9		0.9	

(summarized from Final Study Report, p.61)

A total of 58% of patients in Arm A and 68% in Arm B have progressed while on 5-FU (p=0.0062). A total of 95% and 91% of patients in Arm A and Arm B respectively, progressed while on 5-FU and within 3 months of treatment. This confirms that the population was truly 5-FU resistant and is equally distributed between the two arms.

Sixty-five percent of patients in the CPT-11 arm and 60% of patients in the 5-FU arm have received prior chemotherapy with 5-FU bolus. At the maximum, 35 to 38 percent of the patients were treated with infusional 5-FU.

Table 37. Pretreatment Characteristics (cont'd)

Treatment Arm	Arm A		Arm B	
	N	%	N	%
Number of Patients	189	100	90	100
Patients assessed by 2 imaging procedures	112	88	119	90
Patients assessed by CEA only	15	12	13	10
Patients assessed by both	36	28	32	25
Primary Tumor (%)				
Right Colon	27	21	28	22
Left Colon	45	35	52	40
Rectum	54	42	48	37
Rectosigmoid	1	1	1	1
Prior Therapy				
Prior surgery	126	99	127	98
Prior radiotherapy	23	18	26	20
Number of Organs Involved				
1	61	48	60	47
2	43	34	46	36
3	16	13	21	16
4	5	4	2	2
5	2	2		
Sites of Diseases				
Liver	100	79	98	76
Lung	44	35	53	41
Abdominal mass/lymph nodes	26	20	26	20
Peritoneum	19	15	13	10
Other	31	24	30	23

(Final Study Report, p.54)

For the patients who progressed by CEA only, the increase between two assessments is by a factor of 3. No patient was below the 50% increase required by the protocol.