CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-571/S-008

MEDICAL REVIEW(S)

MEDICAL OFFICER'S REVIEW OF AN NDA SUPPLEMENT

Irinotecan Hydrochloride (Camptosar Injection®)
For Colorectal Cancer
(Application for Full Approval from Accelerated Approval Status)

NDA #	**20-571**
Submission Date:	**April 28, 1998**
Review Completion:	**October 1, 1998**
Sponsor:	**Pharmacia and Upjohn**
Medical Reviewer	**Isagani M. Chico, MD**

MEDICAL OFFICER'S REVIEW OF AN NDA SUPPLEMENT

NDA #20-571 **Submission Date: April 28, 1998**

Sponsor: Pharmacia & Upjohn **Review completed:**

I. GENERAL DRUG INFORMATION

Drug name: CPT-11
Irinotecan Hydrochloride Injection
CAMPTOSAR™ Injection

Generic name: Irinotecan Hydrochloride Injection (CPT-11; U-101440E)

Chemical Name: (4S)-4,11-diethyl-4-hydroxy-9-{(4-piperidinopiperidino)carbonyloxy]-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4H,12H)dione hydrochloride trihydrate

Chemical formula: $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_20$

Molecular Weight: 677.2

Pharmacological Category: Topoisomerase I Inhibitor

Related drugs: Other topoisomerase I inhibitors (topotecan, camptothecin)

Mechanism of Action

CPT-11 is an inhibitor of topoisomerase I, an enzyme responsible for variations in topological form of DNA causing single strand breaks in DNA which prevent its

replication and inhibit RNA synthesis.[1] The cytotoxic effect of CPT-11 and its principal active metabolite, SN-38 is specific for the S-phase of the cell cycle.

Proposed Indication

"Camptosar is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has progressed or recurred following 5-FU based chemotherapy."

II. REGULATORY HISTORY OF CPT-11

Irinotecan was licensed in Japan in September 1995 for the treatment of patients with colorectal cancer. It was approved in France in May 1995 for the treatment of patients with inoperable advanced colorectal cancer previously treated with adjuvant or palliative 5-FU based chemotherapy. Subsequent to approval in the United States in June 1996, CPT-11 has been approved in several other European countries, Canada, Australia, and various Latin American countries.

Table 1. Regulatory History of CPT-11

DATE	EVENT
June 14,1996	Accelerated Approval granted
February 5, 1997	Triple Sponsor Presentation
Dec 17, 1997	Pre-sNDA meeting
Apr 28, 1998	Supplemental NDA submitted
May 14, 1998	D21 FDA Meeting
June 5, 1998	D45 FDA Meeting
September 3, 1998	ODAC Presentation
October 28, 1998	User Fee Date

Details:

June 14, 1996 (Accelerated Approval)

- CPT-11 granted accelerated approval on the basis of tumor response among 503 patients with colorectal cancer whose disease progressed or recurred following 5-FU. It was agreed that Study M/6475/0038 (status of the study discussed in next section) would be the confirmatory trial.

February 5, 1997 (Triple Sponsor Presentation)

- The FDA invited worldwide sponsors of CPT-11: and Pharmacia and Upjohn (U.S.A.) to present summaries of clinical trials in development for CPT-11 in their respective regions.

December 17, 1997 (Pre-NDA Meeting)

P&U proposed the submission of the results of studies instead of the data from M6475/0038, originally committed as the confirmatory trial to obtain full approval of CPT-11 in this indication. The FDA agreed.

May 14, 1998 (D21 FDA Meeting)

- NDA 20-571 was given "priority" (P) designation on the basis of a possible advantage in survival favoring CPT-11.

- Study centers for DSI (Division of Scientific Investigations) audit were determined as follows:

Table 2. Study Centers for DSI Audit, NDA 20-571

STUDY	INVESTIGATOR	NO. OF PATIENTS		TOTAL (%)
		ARM A	ARM B	
STUDY				
UK	Cunningham	25	12	
	James	16	8	**61/279=22%**
STUDY				
Belgium	van Cutsen	12	12	
Italy	Bajetta	10	11	**45/256=18%**

- Requests to the sponsor:
  1. Annotated sample case report forms for studies mapping elements in the electronic database
  2. User dataset descriptions for electronic database tables
  3. Latest versions of the protocols
  4. Strikethrough and proposed final version of the label

June 5, 1998

- Requests to the sponsor:
  1. Items # 1 and 2 from the list of requests dated May 14, 1998 were re-requested.
  2. An alphabetical list of codes/identifiers with corresponding decodes for the electronic database.

July 2, 1998

- Clarification regarding number of study sites: Less study sites in the end compared to study start date in Finland (from 3 to 2) and Ireland (from 2 to 1).

  Clarification: (sent July 27, 1998) One of the study centers in Ireland did not show interest in participating; decided not to open the second center. In Finland, the third study center did not participate.

- Request for a summary report of study M/6475/0038

  Please see next section for the summary. The summary report does not contain any efficacy or safety information.

July 15, 1998

- Clarification regarding the rationale for administration of lower doses of CPT-11 to patients who were >70 years old and those with baseline PS of 2.

  Clarification: (sent July 27, 1998) A multivariate analysis of available Phase II population showed that age and performance status were predictive of Grade 3-4 toxicity (for febrile neutropenia and delayed diarrhea). Therefore, the investigators decided to reduce the starting dose of CPT-11 from mg/m^2 in studies

  In the US phase II experience, age ≥65 years has been associated with a greater risk of CPT-11 induced grade ¾ diarrhea. All patients ≥ 65 years of age treated with mg/m^2 experienced dose limiting diarrhea; while those treated with mg/m^2 did not. These findings confirm the use of a lower starting dose in these patients.

July 17, 1998

- Request to submit copies of "Clinical Experiences Forms" and reports submitted for patients who were hospitalized while on treatment

  Submitted on July 27, 1998.

Phase 4 Study Design and Summary of Results

III. MANUFACTURING CONTROLS

The following considerations regarding drug manufacturing pertinent to this NDA submission are the following: (refer to the chemistry review, Robert Barron, Ph.D., for details)

1. European development of the drug was licensed to while US development was licensed to P&U. The drug product manufactured in Europe undergoes sterilization process while the Upjohn product does not. The facility in Europe was inspected in 1998 for several profile classes, and was found acceptable.

2. The current package insert for the preparation of the infusion solution of CAMPTOSAR states that:

For the dosing regimen proposed, infusion solution concentrations exceed the acceptable range. Additional chemical and physical stability data was provided in the NDA to support stability of infusion solutions up to concentrations of mg/mL. At concentration ranges between mg/mL to mg/mL, 5% Glucose (Dextrose) Injection and 0.9% Sodium Chloride Injection were found to be compatible at room temperature for 24 hours and at refrigerated temperature for four days (4° to 8°C)

- Reconstituted solutions at a concentration of up to mg/mL were stable in glass bottles, PVC bags or PVC tubing with no evidence of leaching.

IV. PHARMACOLOGY

Pharmacokinetics

Every Three Weeks vs. Weekly CPT-11

Based on findings from six phase I and three phase II studies, weekly and every-three- week administration schedules appear to be similar irrespective of dosage schedules and dose of CPT-11 administered.

Table 4. Summary of Range in Mean CPT-11 and SN-38 Pharmacokinetic Parameters in Phase I and II Trials Using the Weekly and Every -Three-Week Regimens of CPT-11

Study No.	Administration Schedule	CL ($L/hr/m^2$)	CPT-11 $t_{1/2}$ (hr)	V_z (L/m^2)	SN-38 $T_{1/2}$ (h)
Phase I Studies					
M/6475/0027	90 min wkly for 4, q6 wks	11.2-18.0	5.7-11.5	--	8.6-28.0
M/6475/0008	90 min wkly for 4, q6 wks	12.9-24.9	--	--	--
DM111	30 min infusion	--	5.0-7.2	--	--
M/6475/0024	90 min q 3 wks	11.6-13.9	11.3-12.3	216-235	18.2-14.4
M/6475/0026	90 min q 3 wks	16.5-27.7	3.9-6.7	104-209	2.8-14.0
RPR CPT-101	30 min q 3 wks	9-26	8.5-31.3	79-226	13.8± 1.4
Phase II Studies					
M/6475/0001	90 min wkly for 4, q6 wks	8.6-9.9	5.0-5.3	69-74	--
M/6475/0006	90 min wkly for 4, q6 wks	13.2-13.2	5.7	107-110	9.8
RPR CPT-205	30 min q 3 wks	15.2	--	--	--

(Table E-1 and Table E-2, vol 1.1)

V. CLINICAL BACKGROUND

Reviewer comment: *Notations identified as "Reviewer comment" and all italicized text represents the FDA reviewer commentary and evaluation of the study. These are found throughout this NDA review to point out differences in the interpretation of study results, discrepancies in the data, or to emphasize certain aspects of the study that maybe relevant to the marketing approval and/or the approved labeling of CPT-11.*

Introduction

There is no standard salvage treatment for patients in whom 5-FU based chemotherapy has failed. The median survival for such patients was estimated to be 4 to 8 months. No randomized study has been conducted with best supportive care as the control arm. However, reports have demonstrated that some patients may benefit from second-line infusional 5-FU after failing bolus treatment.[2] This could be due to the schedule, the high dose intensity or both.

5- FU Infusion Schedules and Results of Studies

The following table summarizes response rates from several Phase 2 trials using different 5-FU infusion schedules in patients with recurrent colorectal cancer:[3]

Table 5. Infusional 5-FU Schedules

Dosing Schedule	Response Rate	Dose Intensity ($g/m^2/wk$)
24-hr CIVI wkly	25%	2.6
48-hr CIVI wkly or q 2 wks	30%	2.4
120-hr CIVI q 4-5 wks	3%	1.25
14-days CIVI	12%	1.225
Protracted infusions ≥ 10 wks	30%	2.1

Summary of Overall Response Rate in Phase II Studies of CPT-11

In four Phase 2 studies, 363 patients selected for 5-FU resistance and treated with CPT-11 at 350 mg/m^2 q 3 weeks showed a median response rate of 12.9% (C.I. 9.7-16.8) and a tumor stabilization rate of 41.1%. Median duration of response was 33 weeks (7.6 months, range 18-53+).

Table 6. Overall Response Rate in Eligible Patients of Phase II Studies (as of June 96)

Study	No. of Pts	CR	PR	NC	PD	NE	Response Rate (95% C.I.)
205	62	1	9	15	32	5	16.1 (8.0-27.7)
V222	95	0	13	42	34	6	13.7 (7.5-22.3)
F220	99	0	12	51	28	8	12.1 (6.4-20.2)
F221	107	1	11	45	42	8	11.2 (5.9-18.8)
TOTAL	**363**	**2**	**45**	**153**	**136**	**27**	**12.9 (9.7-16.8)**

(Final Study Report, , Table 1, vol 1.13.)

Reviewer's comment: *These results are consistent with the response rates in patients from the three Phase II trials considered in the original NDA application (confidence intervals overlapping) as shown in Table 7 below.*

Table 7. Response Rates from Three Pivotal Phase 2 Studies (weekly x 3 every 4 weeks schedule)

Study	Dose (mg/m^2) wklyx3 q 4 wks	No. of Pts	CR+PR	Response Rate (95% C.I.)
0001	125/150	48	10	20.8 (9.3,32.3)
0003R	125	90	12	13.3 (6.3, 20.4)
0006	100	102	8	7.8 (2.6, 13.1)
	125	64	8	12.5 (4.4, 20.6)
TOTAL		**304**	**38**	**12.5 (8.8, 16.2)**

Reviewer comment: *Table 8 contains updated efficacy results (response rates, survival) not available when the original NDA was reviewed. All the patients were off-study at the cut-off date of March 1, 1998.*

Table 8. Sponsor's Summary of Efficacy Results with Second-line 5-FU Treatment from Pivotal Trials for CPT-11

	ORIGINAL NDA			CURRENT NDA			
Treatment Schedule	125 mg/m^2 weekly x 3			350 mg/m^2 every 3 weeks			
Study No.	0001	0003R	0006				
Therapy	CPT-11	CPT-11	CPT-11	CPT-11	BSC	CPT-11	5-FU
N	39	90	64	189	90	127	129
Response Rate (%) (95% C.I.)	20.5	13.3	14.1	--	--	--	--
1-Yr. Survival	41	31.1	45.2	36.2 (29.3-43.1)	13.8	44.8 (36.2-53.4)	32.4 (24.3-40.5)
Survival (months) (range)	9.7	8.1	10.7	9.2	6.5	10.8	8.5

Reviewer's comment: *The primary efficacy endpoint in protocols 001, 003 and 006 in the original NDA application was response rate. Survival was not a prospectively defined endpoint. As single arm trials, the effect of CPT-11 on*

survival would be difficult to assess without concomitant control groups. In addition, these data need to be verified and should be interpreted with caution.

VI. SUMMARY OF NDA CONTENTS

Table 9. Scope of sNDA 20-571

	No. of Studies	No. of Pts	*Location of Discussion in NDA Review*
RPR Phase 3 Study V301	2	279	p. 18-47
RPR Phase 3 Study V302		256	p. 48-82
Other Supportive Information			
P&U Phase I Study 024	1	34	p. 85
Phase I Study	1	120	p. 86
Efficacy Update Report of P&U Studies	3	304	p.16
Phase II Studies	2	320	p. 88
Cholinergic Effects Report	4	356	p.88

(Item 3, Application Summary, vol. 1.1)

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V. CLINICAL PROTOCOLS

Study

This is a non-blinded, randomized, multicenter phase III study comparing CPT-11 plus BSC to BSC alone in metastatic colorectal cancer after failure of treatment with 5-FU. The study was designed for 2:1 randomization (CPT-11+BSC vs. BSC) with no crossover.

***Reviewer's comment**: The following section contains excerpts from the final version of the protocol. All protocol amendments were instituted in February 7, 1996, and are highlighted in the body of the protocol below.*

Title:

A Randomized Phase III Multicenter Trial Comparing Irinotecan Hydrochloride Trihydrate Plus Best Supportive Care to Best Supportive Care Alone in Patients with Metastatic Colorectal Cancer After Failure of Treatment with 5-fluorouracil

Principal Investigator:

David Cuningham, MD
Department of Medicine
Royal Marsden Hospital, UK

Study Centers

48 centers in the following countries: U.K.: 19, Ireland: 1, Finland, 2; Norway:3, Sweden:7, The Netherlands:4, Lebanon:2, Slovakia:2, Republic of South Africa:4, Hungary:3, Israel:1 (before: 25 centers: U.K.10, Ireland: 2, Finland: 3, Norway: 3, Sweden:4, Netherlands:3)

***Reviewer's comment**: Two study centers located in the U.K. (Investigators: Dr. Cunningham and Dr. James) comprising 22% (61/279) of the total study population were selected for audit by DSI.*

Study Period

September 13, 1995 to June 30, 1997
Amendment 1: February 7, 1996

***Reviewer comment**: A total of 76 patients (27%)have been enrolled in the study on February 7, 1998.*

Objectives

Primary:

To compare the **survival** after treatment with CPT-11 plus best supportive care and after treatment with best supportive care alone in patients with metastatic colorectal cancer who have previously failed a 5-fluorouracil containing regimen

Secondary:

To compare the **quality of life and other clinical benefit parameters**, the **toxicity and symptomatology** in patients treated with CPT-11 plus best supportive care against best supportive care alone.

An independent **socioeconomic** study was to be conducted in parallel with the clinical study. Appropriate modules for every 3 week data collection were included in the CRF. (before: ... every 6 week data collection ...)

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 25% on 2 consecutive CEA values with at least one month interval between each sample. A third confirmatory CEA value which should be equal to or greater than the second will be required to validate the 25% increase. (before: progressive increase of at least 25% on 3 consecutive CEA values with at least one month interval between each sample but with no more than 6 months between the first and last sample)

***Reviewer's comment**: The original protocol required more rigorous criteria for progression since values had to increase progressively by 25% in each of the three measurements. In the amended version of the protocol, an increase of 25% in CEA on two occasions was sufficient.*

The ASCO Recommendations for the use of tumor markers in colorectal cancer states that "there is insufficient data to recommend use of serum CEA alone in monitoring response to treatment. If no other simple test is available to indicate a response, CEA should be measured at the start of treatment for metastatic disease and every 2 to 3 months during active treatment. Two values above baseline are adequate to document progressive disease, even in the absence of corroborating radiographs."[4]

For review of clinical trials, the FDA does not rely on measurement of CEA alone as adequate for establishing progression of disease. For studies follow-up of CEA for tumor response was not a major concern since survival was the primary efficacy endpoint.

- Relapsed with metastatic disease while receiving a 5-FU containing regimen or within six months after the last 5-FU infusion of a 5-FU containing regimen. The intent of 5-FU could be adjuvant or palliative

  ***Reviewer's comment**: The indication for CPT-11 is for patients whose disease has progressed or recurred following 5-FU chemotherapy. This implies wider use regardless of the intent of prior 5-FU chemotherapy (adjuvant vs. metastatic), refractoriness of the disease to 5-FU (progression during or within 3-6 months of treatment vs. progression six months or longer after treatment). A majority of patients enrolled in studies may have more resistant disease since they progressed while taking 5-FU or within 3-6 months of adjuvant or chemotherapy for metastatic disease.*

- Time between documentation of progression and randomization must not exceed 3 months
- 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
- The overall number of prior chemotherapy regimens must not exceed three if one of them was given in an adjuvant intent and must not exceed two if only palliative regimens were given
- Either measurable or non-measurable disease provided that the CEA is increased
- 18-75 years old
- WHO Performance status ≤ 2
- Written informed consent
- Adequate hematologic, renal and hepatic functions

(1) ANC ≥2.0 x 10^9/l platelets ≥ 100x10^9/L

(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 two regimens of palliative chemotherapy for advanced and/or metastatic disease
- Previous treatment with topoisomerase I inhibitors
- Bulky disease defined as more than 50% of liver involvement or more than 25% lung involvement or abdominal mass (excluding hepatic tumors) ≥10 cm (before: palpable abdominal mass ≥10 cm)
- Presence or history of CNS metastases
- Unresolved bowel obstruction or subobstruction/diarrhea
- Chronic diarrhea
- Other serious illness or medical condition such as 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
- Past or current history of neoplasm other than colorectal carcinoma, except for cured non melanoma skin cancer or in situ carcinoma of the cervix
- Concurrent treatment with other experimental drugs or within a clinical trial (starting one week prior to randomization) (before: at baseline and within 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 randomized to Arm B (BSC)

Work-up

Table 10. Baseline Investigations, Study

INVESTIGATIONS	TIMING
History/P.E.	≤ 7 days of randomization
Hematology (CBC, PT/PTT) Biochemistry (alk phos, LDH, AST, ALT, creatinine, protein)	≤ 7 days of randomization, (added: ≤ 7 days of prior to visit/cycle1)
Tumor Measurements (CEA, CT scans)	≤28 days prior to randomization (before: ≤ 14 days)
Quality of Life	≤14 days prior to randomization, prior to CPT-11 infusion

Table 11. On Study Investigations, Study

INVESTIGATIONS	TIMING
History/P.E.	Arm A[1]: q 3 weeks or Day 1 Arm B[2] q 3 weeks
Concomitant Therapy (list of all therapeutic measures on a BSC basis)	Arm A: q 3 weeks or Day 1 Arm B: q 3 weeks
Hematology (CBC, PT/PTT)	Arm A: Days 1,8 and 15 Arm B: as indicated
Biochemistry (alk phos, LDH, AST, ALT, creatinine, protein)	Arm A: Day 1 Arm B: as indicated
Tumor Measurements: CT scans (added: or appropriate imaging) ± CEA	Arm A and B: as indicated
Quality of Life Socio-economic data	after 3 and 6 weeks on study, then every 6 weeks q 3 weeks or Day 1 for Arm A (before: q 6 weeks)

Arm A: CPT-11 + BSC Arm B: BSC

***Reviewer's comment**: Comparisons of events with evaluations that are done at regular and equal intervals for both arms (e.g., history and P.E., QOL assessments) would be more reliable compared to evaluations in which the frequency of follow-up is not similar (e.g. Tumor Measurements, CBC, chemistry).*

Study Treatment

Arm A: CPT-11, 350 mg/m^2 (capped total dose: 700 mg/m^2) as a 90-minute intravenous infusion on day 1 every three weeks + BSC.

- Treatment with CPT-11 within one week of randomization.
- (added: The starting dose for patients aged ≥ 70 years or performance status =2 should be reduced to 300 mg/m^2. The total dose of CPT-11 should not exceed a total dose of 700 mg/m^2.)
- After discontinuation of treatment with CPT-11, the patients will be treated with BSC alone

Arm B: Best Supportive Care (BSC)

Patients enrolled in both arms will receive the best supportive care available, according to institutional standards. This may include antibiotics, analgesics, transfusions, corticosteroids, assistance of a psychotherapist or any other symptomatic therapy (except CPT-11 or other topoisomerase I inhibitor) as medically indicated. Localized radiation therapy to alleviate symptoms such as pain is allowed provided that the total dose delivered is in the palliative range.

Further antitumor therapy after failure of CPT-11 (except experimental new drugs) can be administered if deemed necessary to control disease related symptoms and is in accordance with the institutional standard for BSC.

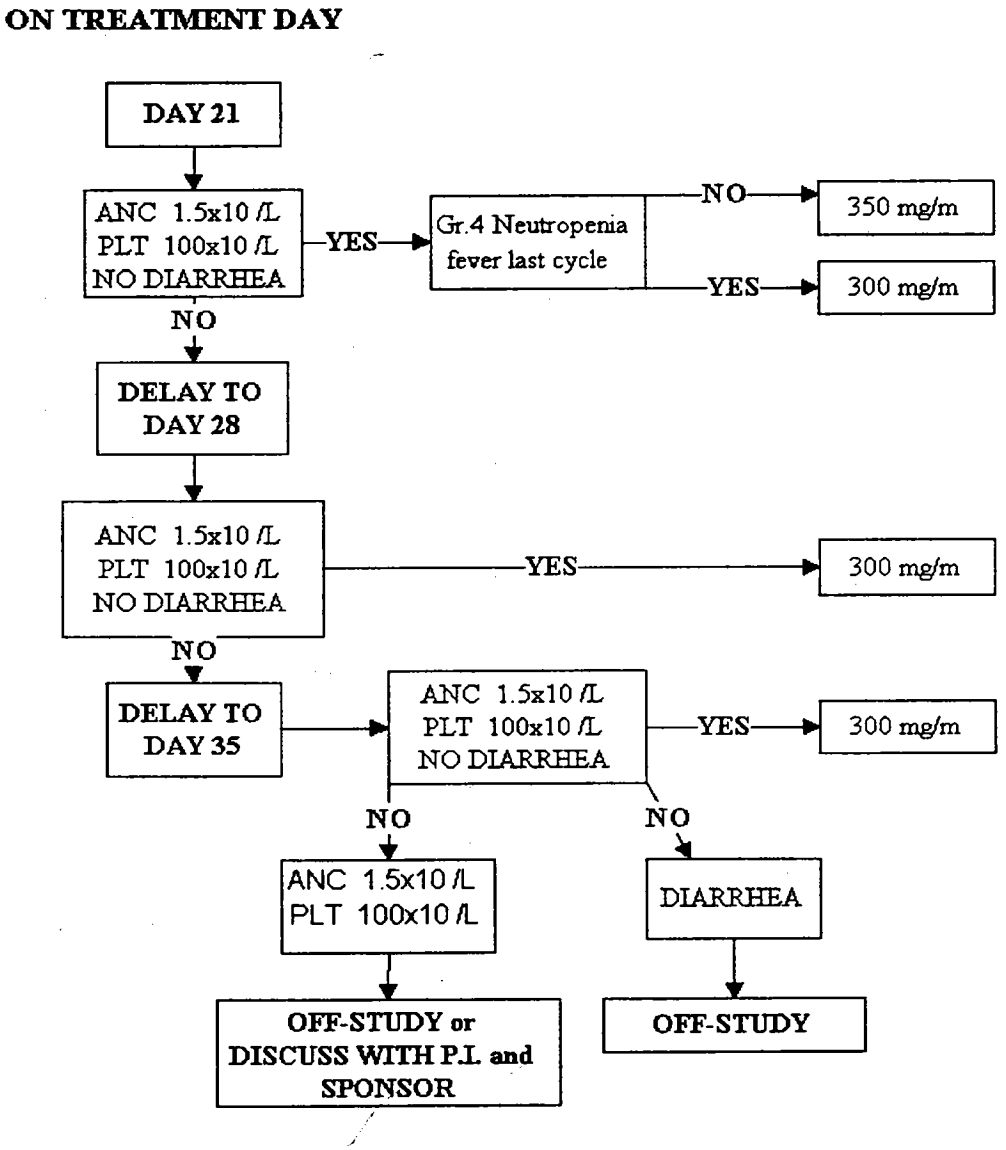
***Reviewer comment**: Study investigators were queried regarding institutional standards for BSC using two types of forms. Form A includes questions that were open-ended and allowed description of the institution's principles for BSC and listing of individual agents used for a specific symptom. Eleven investigators used Form A. None of these investigators indicated the use of chemotherapy as part of BSC. Thirty-seven investigators responded using Form B. This did not require a comprehensive description of the institution's BSC practice but allowed the investigators to pick answers among choices provided. However, it specifically inquired whether use of antitumor drugs was part of the BSC regimen. Of the 37 investigators, 19 used antitumor agents, the most common reason being for control of cancer -related symptoms such as pain, etc. The following antitumor agents were described as part of the BSC arm:*

5-FU: 10 investigators	*Adriamycin/anthracyclines: 2*	*Carmofur: 1*
Mitomycin-C: 10	*BCNU: 1*	*Ph I agents: 1*
Methotrexate: 2	*Etoposide: 1*	
Tomudex: 2	*Cisplatin: 1*	

Dose Modification:

In general, treatment with CPT-11 may be delayed for up to two weeks. Dose adjustments are to be made according to the system showing the greatest degree of toxicity using the NCI common toxicity criteria.

Figure 1. FDA Schema for Treatment and Dose Modification, Study



Hematologic Toxicity: In case of grade 4 neutropenia with or without febrile neutropenia, the dose of CPT-11 will be reduced to 300 mg/m^2 in subsequent courses. If in spite of this reduction, grade 4 neutropenia (added: or febrile neutropenia (fever ≥ 38° and grade 3 or 4 neutropenia) occurs again, the treatment will be terminated, unless justified. In this case, the treatment will be continued at 250 mg/m^2.

Diarrhea: A dose reduction may be initiated in the event of severe diarrhea (i.e. grade 4 or grade 3 requiring IV hydration), despite suitable symptomatic treatment. If diarrhea is ongoing on day 21, delay treatment for a maximum of two weeks. If no recovery occurs after 2 weeks delay, the patient will go off therapy but followed until resolution of diarrhea. Only two dose reductions will be allowed per patient. (before: In the event of persistent grade 3 diarrhea for more than 2 weeks, despite suitable symptomatic treatment, the CPT-11 treatment will be terminated and the patient followed up to resolution of diarrhea. If diarrhea is still ongoing on day 21, delay treatment for a maximum of two weeks. If no recovery occurs after two weeks delay, the patient will go off therapy.)

Up to two weeks delay may be allowed for other toxicity ≥ grade 2 on day 21 with dose reduction in 50 mg/m^2, increments until a dose of 250 mg/m^2 is reached.

Concomitant Treatments

Table 12. Concomitant Treatments, Study

Atropine	• for acute severe cholinergic symptoms including early diarrhea, sweating, hypersalivation, visual disturbances, lacrimation • systemic prophylaxis may be given on any cycle
Loperamide	• 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
Fluoroquinolone	• for persistent diarrhea > 24 hours despite recommended loperamide treatment. Continue oral rehydration
Antibiotics	• prophylaxis after grade 4 neutropenia ± fever may be given but not recommended routinely
	• not recommended but may be considered

Treatment Discontinuation

- Toxicity
- Disease progression
- Patient refusal

Follow-up

For Arms A and B: Every three weeks up to one year to document:

- survival
- disease related signs and symptoms
- quality of life, and

For Arm A only:

- resolution of all CPT-11 side effects, if any
- tumor progression if CPT-11 was stopped before progression

There was no specific follow-up schedule after one year.

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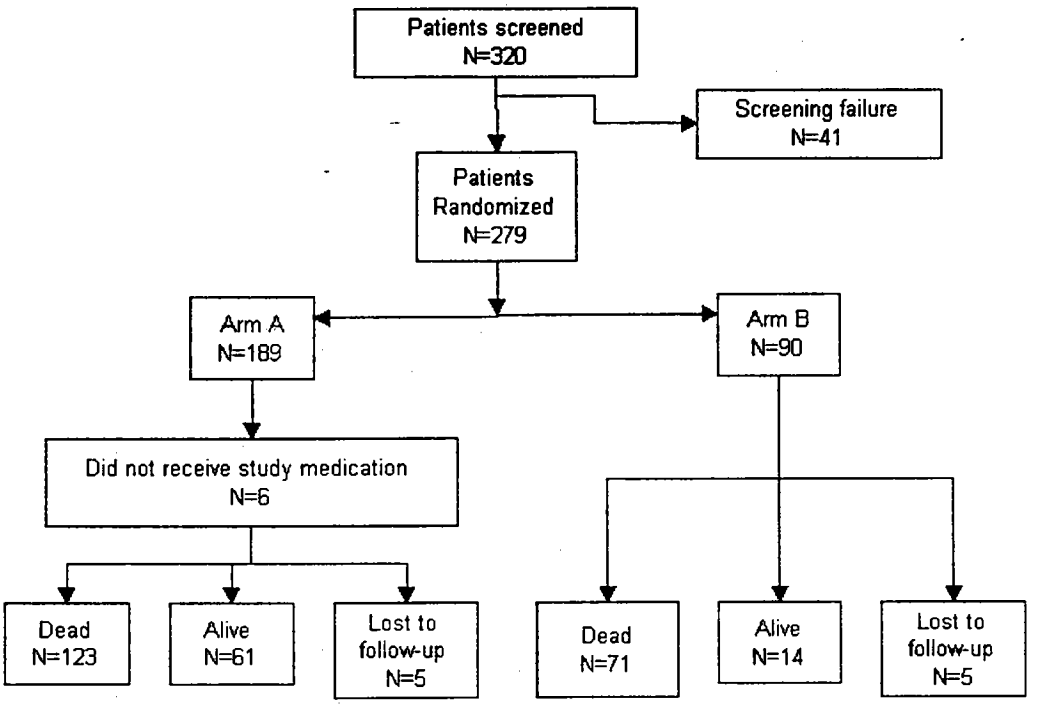
Results

Patient Disposition

Figure 2. Disposition of Patients as of June 30, 1997



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Forty-one (13%) of the 320 patients screened for inclusion were not randomized for the following reasons:

Table 13. Reasons for Non-Randomization, Study

REASON	NUMBER (N=41)
Refused by Monitoring Committee	11
No documented progression	6
Missing information	6
Laboratory values not as per protocol	4
Bulky disease	3
History of other cancers	3
Patient intending to withdraw if randomized to Arm B	3
Non-metastatic disease	2
No informed consent	1
Contraindication to study drug	1
CNS metastases	1

(Study Report, , p48)

Of the 189 patients enrolled in Arm A, 169 discontinued treatment for the following reasons:

Table 14. Reasons for Treatment Discontinuation in Arm A, Study (N=189)

	N	(%)
Consent withdrawn, refused further treatment	14	7.4
Non-fatal progressive disease	125	66.1
Non-fatal toxicity	10	5.3
Death due to toxicity	2	1.1
Death due to progressive disease	9	4.8
Death due to other reasons	1	0.5
Lost to follow-up	1	0.5
Other reasons	7	3.7

(Final Study Report, vol. 1.13 p.6)

There were 12 cases of treatment discontinuation due to drug toxicity, two were fatal, and ten were non-fatal. The reason for termination was due to one or a combination of toxicity such as diarrhea, asthenia, febrile neutropenia, infections, anorexia and neurologic symptoms.

Patients were taken off study for the following reasons: consent withdrawn, any cause of death, lost to follow-up, and patients having reached the cut-off date or having completed one year on study, and those classified under other.

Table 15. Reasons for Study Discontinuation

	SPONSOR'S ANALYSIS		*FDA ANALYSIS*	
	Arm A N=189	**Arm B** N=90	***Arm A*** *N=189*	***Arm B*** *N=90*
	N (%)	N (%)		
Consent withdrawn	37 (19.6)	17 (18.9)	*37*	*16*
Death due to toxicity	2 (1.1)[a]	NA (NA)	*94*	*56*
Death due to PD	91(48.1)	54 (60)		
Death: other reasons [b]	1 (0.5)	2 (2.2)		
Lost to follow-up	5 (2.6)	5 (5.6)	*5*	*5*
Completed 1 year/ reached cut-off date	52 (27.5)	12 (13.3)	*53*	*12*
Other[c]	1 (0.5)			*1*

[a]Death due to toxicity — 10904A: diarrhea and asthenia; 05211A: neutropenic sepsis

[b]Death: other reasons — 12301A: cardiac insufficiency; 02207B: CVA; 12202B: intestinal obstruction

[c]Other — 02201A: refused further ff-up

(Final Study Report, p.50)

***Reviewer's comment**: Based on review of the electronic data and summary listings, the FDA analysis of the reasons for study discontinuation generally tallied with the sponsor's.*

The number and frequency of clinic visits by patient in each arm are summarized in the following table:

Table 16. Patient visits

	Arm A	Arm B
Number of Patients	189	90
Total number of visits	1690	568
Number of visits by patient		
Median	9.0	5.0
Mean	8.9	6.3
Time between two visits (day)		
Median	21.0	21.0
Mean	24.1	25.9

(Final Study Report, vol. 1.13 p.6)

Reviewer's comment: *The interval between visits is similar in both arms but the median number of visits was greater for patients enrolled in Arm A. This may impact on the comparability of data (e.g. physical examination findings, QOL testing, etc).*

Randomization Procedure

Using a 2:1 randomization, A total of 264 patients were estimated (176 patients in the CPT-11 + BSC arm: Arm A, and 88 patients in the BSC alone: arm: Arm B) to have a 0.8 power to show a significant difference in the one-year survival rates of 35% vs. 20%, respectively). A total of 279 patients (189: Arm A and 90: Arm B) were enrolled. An Independent Monitoring Committee (IMC) composed of three oncologists not participating in the study was placed to regularly assess eligibility, safety, efficacy ethical issues in the study.

Patients were stratified by study center and randomized centrally in blocks of 6 patients (4 in Arm A and 2 in Arm B) in the RPR offices of Antony (Paris, France). However, stratification by center was not accomplished due to a small number enrolled in some centers.

Table 17. Protocol Deviations

At Randomization	ARM A N=189		ARM B N=90	
Patients	N	%	N	%
Current cancer other than colon or rectum	1	0.05	--	--
Progressive disease > 6 months after 5-FU	5	2.6	--	--
Progression not documented	15	7.9	9	10
Randomization not within 3 months of last PD	8	4.2	5	5.6
>2 palliative ± 1 adjuvant	4	2.1	3	3.3
Previous history of other cancer	1	0.5	--	--
Bowel obstruction/subobstruction	2	1.1	--	--
Bulky disease	4	2.1	4	4.4
Lab value outside specific range	7	3.7	3	3.3
Deviations During Study in Arm A				
First Infusion of CPT-11 later than 8 days after randomization	17	9	NA	NA
Incorrect dose at cycle 1	45	24	NA	NA
Never treated	6	3.2	NA	NA

(Study Report, p52-53)

Reviewer's comment: *For patients whose disease progression were not documented, radiologic imaging was performed between six and up to 17 months before start of treatment.*

Patient Demographics

Table 18. Pretreatment Characteristics

Treatment Arm	Arm A		Arm B	
	N	%	N	%
Number of Patients	189	100	90	100
Male/Female (%)	129/60	68/32	52/38	58/42
Performance Status (PS)				
0	89	47	28	31
1	73	39	41	46
2	26	14	21	23
Unknown	1	0.5	--	--
PD while on 5-FU	133	70	57	63.3
PD ≤ 6 months	50	26	32	36
PD ≥ 6 months	5	3	0	0
Intent of Prior Chemo				
Adjuvant only	18	10	15	17
Palliative± Adjuvant	125	66	52	58
2 Palliative ± Adjuvant	40	21	20	22
>2 Palliative ± Adjuvant	4	2	3	3
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)	19.3		17	
Median time from progression to randomization (months)	1.0		1.0	
Median time from last 5-FU Infusion to Randomization (months)	1.4		1.6	

(summarized from Final Study Report, p.54)

Reviewer's comment: *Using Chi-square test of PS 0, 1, and 2, there was a statistically significant imbalance (p=0.02) in the performance status of patients in favor of Arm A. However, Fisher's exact test comparing PS 0+1 vs. 2 did not yield statistically significant differences with a p-value of 0.06. Such grouping of patients seems to carry more prognostic significance in this disease.*

It appears that patients who were treated with CPT-11in Arm A have disease that are more refractory to 5-FU compared to patients in Arm B, although the differences were not statistically significant. The response rates were 23% (Arm A) vs. 32% (Arm B) and patients who received 5-FU as adjuvant treatment were also less in Arm A (10% vs. 17%).

Table 19. Pretreatment Characteristics (cont'd)

Treatment Arm	Arm A		Arm B	
	N	%	N	%
Number of Patients	189	100	90	100
Patients assessed by CEA only	27	14	9	10
Primary Tumor (%)				
Right Colon	40	21	18	20
Left Colon	61	32	27	30
Rectum	76	40	38	42
Rectosigmoid	9	5	5	6
Prior Therapy				
Prior surgery	188	99	88	98
Prior radiotherapy	49	26	24	27
Number of Organs Involved				
1	82	43	42	47
2	75	40	31	34
3	27	14	13	14
4	4	2	4	4
5	1	1	0	0
Sites of Diseases				
Liver	151	80	69	77
Lung	69	36	27	30
Abdominal mass/lymph	36	19	27	30
nodes	13	7	9	10
Peritoneum	56	30	27	30
Other				

(summarized from Final Study Report, p.54)

***Reviewer's comment**: In a Phase I study which evaluated patients with solid tumors who had received prior chemo- and/or radiotherapy, the MTD was 290 mg/m^2 in patients with prior pelvic/abdominal radiation. The DLTs were gastrointestinal events and leukopenia/neutropenia. Since 26% of patients in Arm A received radiotherapy, their tolerance of the recommended dose of CPT-11 in this study is a concern.*