MEDICAL OFFICER SUMMARY STATEMENT FOR THE ADVISORY COMMITTEE

Irinotecan Hydrochloride (Camptosar Injection[®])
For Colorectal Cancer
(Application for Irinotecan as a Component of First-line Therapy of Patients with
Metastatic Carcinoma of the Colon or Rectum)

NDA #	**20-571/SE1-009**
Submission Date:	**October 20, 1999**
Sponsor:	**Pharmacia and Upjohn**
Medical Reviewer	**Isagani M. Chico, MD**

The following document contains a summary of review findings.
Additional analyses and updates may be provided at the time of the
Advisory Committee presentation.

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LIST OF ABBREVIATIONS

5FU	5-fluorouracil
ANC	absolute neutrophil count
B5-FU	Best Estimated 5-FU Based Chemotherapy Regimen
BSC	Best Supportive Care
CEA	carcinoembrionic antigen
CNS	central nervous system
CPT-11	Irinotecan Hydrochloride
CR	complete response
CRF	case report form/s
CVA	Cerebrovascular Accident
DSI	Division of Scientific Investigations, FDA
CT	computer tomography
G-CSF	Granulocyte Colony Stimulating Factor
GM-CSF	Granulocyte-Macrophage Colony Stimulating Factor
IMC	Independent Monitoring Committee
IV	intravenous
LV	leucovorin
PD	progressive disease
PR	partial response
P&U	Pharmacia and Upjohn
q 6 wks	every 6 weeks
RPR	Rhone Poulenc Rhorer
QLQ	Quality of Life Questionnaire
SC	subcutaneous
WHO	World Health Organization
wk	week
wkly	weekly

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: $C_{33}H_{38}N_4O_6 \bullet HCl \bullet 3H_2O$

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 as a component of first-line therapy for patients with metastatic colorectal cancer."

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[1] D'Arpa P. Topoisomerase targeting antitumor drugs. Biochem Biophys Acta 989, 163-167, 1989

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
6/14/96	Accelerated Approval for treatment of recurrent or progression of colorectal CA following 5-FU based therapy. Confirmatory trial agreed upon was Study 0038 (untreated metastatic CA)
10/22/98	Full approval granted based on two Phase 3 trials (V301 and V302) showing a significant survival advantage in the treatment group)
10/20/99	SNDA for first line therapy submitted

III. CONSULTS / OTHER REQUIREMENTS

DSI Audits

The following sites from Study 0038 were chosen for DSI Audit. The reports from these audits will follow.

1. Lee Rosen, UCLA, Los Angeles CA   11 responders/ 30 patients
2. Leonard Saltz, MSK- New York, NY   14 responders/42 patients
3. Timothy Moore, Columbus CCOP, OH   7 responders/15 patients

Financial Disclosure Statements:

- Certifications for investigators in Study 6475/0038 were obtained from 450 of the 614 investigators (73%). Dr. Leonard Saltz (who established the safety of the Saltz regimen used in one of the arms in Study 0038) submitted a statement showing absence of conflict.
- A total of 118 investigators (90% out of 131) in Study V303 who responded declared absence of conflict.

> *Reviewer's comment: The financial disclosure statement by the investigator is an attempt to assure that the study results are not biased through financial involvement by the investigators with the sponsor. In both studies, the investigators who contributed the most number of patients responded to the request, and did not appear to have a conflict of interest. The sponsor also placed additional controls to assure data integrity by assigning an independent panel to perform blinded response assessments and by not allowing investigators access to the study results while it was ongoing. This seems adequate.*

V. CLINICAL BACKGROUND

The two pivotal trials contain several different 5-FU/LV regimens both as control and as a component of the treatment arm. It is important to evaluate the literature for evidence of efficacy for these regimens. The table below shows the regimens that were used in the control arms of the pivotal trials. The most commonly used regimens in the U.S. are the Roswell Park and the Mayo Clinic Regimens.

Table 2. Control Arms: Pivotal Trials

Name	Dose and Schedule	COMMENTS
Study 0038		
Mayo Clinic (daily x5)	5-FU iv bolus 425 mg/m^2 FA iv infusion 20 mg/m^2 D1-5, q 4weeks	-Arm C, Study 0038 -widely used in the US -approved regimen
Roswell Park (weekly X 6)	5-FU 500-600 mg/m^2 LV 500 mg/m^2 Weekly x 6weeks, q 8 weeks	-widely used in the US
Study V303		
DeGramont[2] (biweekly)	FA 200 mg/m^2 over 2h, then 5-FU iv bolus 400 mg/m^2 + 5-FU 600 mg/m^2 over 22 h D1,2 q 2 weeks	Arm B, Study v303
Weekly High Dose (AIO)[3]	FA 500 mg/m^2 over 2 h, then 5FU 2600 mg/m^2 over 24 h q wk x 6 then 2 weeks rest	Arm A, Study v303

Two of the most popular 5-FU bolus administration schedules were used, in full or in part, in Study 0038. The approved standard of care, the Mayo Clinic regimen was used in Arm C as the control. Literature reports suggest similar efficacy as the Roswell Park regimen. Arm B of Study 0038 combined weekly administration of Camptosar with four of the six weekly 5-FU/LV bolus injection. The following table is a summary of the efficacy comparisons of the 5-FU/LV bolus ichedules from randomized trials.

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[2] Bosset JF, DeGramont, et.al. Randomized phase III trial comparing 5-FU bolus and low dose leukovorin versus 5-FU bolus plus continuous 5-FU infusion and high dose leukovorin in metastatic colorectal cancer. EJC 1995, vol 31A, Suppl.5

[3] Weh H, Wilke HJ, et.al. Weekly therapy with folinic acid and high dose 5FU 24 infusion in pretreated patients with metastatic colorectal carcinoma. Annals Oncol. 1994, 233-237

Table 3 Randomized Citations of the Mayo Clinic versus the Roswell Park 5-FU/LV Regimens

Citation	Regimens	N	RR (%)	TTP (mo)	OS (mo)
NCCTG Buroker[4] 1994	Mayo Clinic: 5-FU 425 mg/m² d1-5, q 4-5 wks LV, 20 mg/m², d 1-5, q 4-5 wks	183	35	5	9.3
	Roswell Park: 5-FU 600 mg/m², wklyx6 q 8 wks LV, 500 mg/m², wklyx6 q 8 wks	179	31	6	10.7
Leichman[5] 1995	Mayo Clinic: 5-FU 425 mg/m² d1-5, q 4-5 wks LV, 20 mg/m², d 1-5, q 4-5 wks	85	17	6	14
	Roswell Park: 5-FU 600 mg/m², wklyx6 q 8 wks LV, 500 mg/m², wklyx6 q 8 wks	86	14	6	13

These studies showed that response rate, time to tumor progression and overall survival were similar between the two regimens. Palliative effects assessed by relief of symptoms, improved performance status and weight gain were also similar. There were significant differences in toxicity with more leukopenia and stomatitis with the Mayo Clinic Regimen, but more diarrhea and requirement for hospitalization to manage toxicity with the Roswell Park regimen. (Buroker, 1994) These schedules were tested in another randomized trial in patients with previously untreated metastatic colorectal cancer (Leichman, 1995). Efficacy results were similar with time to tumor progression of approximately 6 months.

In a meta-analysis by the Advanced Colorectal Meta-Analysis Project of 9 trials, there was a response rate of 23% in patients who were treated with 5-FU/LV and 11% in patients given 5-FU alone.   Survival differences were not seen between these two groups nor was there a statistically significant difference observed between the 5-FU/LV in trials of weekly 5-FU nor in trials of monthly courses.[6]

> ***Reviewer's comment****: The use of the approved Mayo Clinic Regimen as a control arm in this trial seems appropriate.*

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[4] Buroker, T, et al. Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of adcanced colorectal cancer. J Clin Oncl 1994, vol 12, 14-20

[6] Advanced Meta-analysis project, J Clin Oncol, vol 10, No.6 1992, pp896-903

The CPT-11+ 5-FU/LV Arm of Study 0038 (Arm B, Saltz Regimen) was tested in a Phase 1 study at the MSKCC (Saltz). This schedule was modeled after the Roswell Park regimen, with consideration of serious overlapping toxicities between CPT-11 and 5-FU. The 5-FU/LV in the Saltz regimen is less 5-FU dose intensive and is given weekly for four weeks (simultaneously with weekly CPT-11) compared to the Roswell Park regimen where 5-FU/LV is given weekly for six weeks.

> *Reviewer's comment: One of the concerns regarding this study was the uncertainty of the contribution of CPT-11 in Arm B (combination arm) and the possibility that any difference in efficacy might have been solely due to 5-FU/LV. The FDA reviewer agrees with the sponsor's justification using dose and dose intensity comparisons. The weekly dose and dose intensity of 5-FU/LV in study 0038 (500 mg/m2 x 4 weeks) are lower compared to the Roswell Park regimen (600 mg/m2 x 6 weeks). Unless the Roswell Park regimen is exceedingly toxic, it is unlikely that the contribution of the 5-FU/LV alone in Arm B would be more efficacious. This gives an assurance that the activity of Arm B may not just be due to the 5-FU/LV component but possibly in addition to CPT-11.*

In order to assess the efficacy and toxicity afforded by biochemical modulation or schedule variation of 5FU, SWOG designed a phase 2 study comparing 7 different schedules or modulations of 5FU in first line chemotherapy patients with metastatic colorectal cancer.[7] Bolus administration of 5-FU was associated with more frequent grade ¾ hematological toxicity (47%) than infusion based regimens (1-11%) and weekly bolus. Grade 3 and 4 diarrhea was seen most frequently in the weekly bolus regimen with high dose LV and lower but similar in incidence in the infusion groups. Note that the high dose infusional regimens popular in Europe were not included. The following table summarizes the response and survival results from this study:

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[7] Leichman C, Macdonald J, et al. Phase 2 study of fluorouracil and its modulation in advanced colorectal cancer: a southwest oncology group study. J Clin Oncol. 1995, Vol 13, No. 6: 1303-1311

Table 4. Summary of the Efficacy Results of a 7-Arm Trial on 5-FU Modulation and Different Infusion Schedules

Regimen	Response Rate (%) (95%CI)	Median Survival(mos)
5-FU bolus	29 (17-41)	14
5-FU bolus + low dose LV	27 (16-39)	14
5-FU bolus + high dose LV	21 (11-32)	13
5-FU CIVI	29(19-43)	14
5-FU CIVI + low dose LV	26 (15-39)	15
24-hr 5-FU + PALA	25 (14-36)	11
24-hr 5-FU	15 (7-25)	15

Reviewer's comment: Variations in 5-FU modulators or 5-FU administration schedule did not result in differences in survival.

The efficacy of intravenous infusion of 5-FU was compared in a meta-analysis with bolus administration in advanced colorectal cancer.[8] The studies considered for this analysis are shown below:

Table 5. 5-FU CI versus 5-FU Bolus

Trial	5-FU (mg/m^2) CIVI	5-FU (mg/m^2) Bolus	# Pts.
ECOG	300 /day continuously	500 d1-d5, then 600 q 7 days	324
NCIC	350/day, d1-d15 q 28 days	400-450 d1-5, q 28 days	185
SWOG	300/day, d1-d28 q 35 days	500 d1-d5, q 35 days	181
MAOP	300/day continuously	500 d1-d5, q 35 days	173
France	750 d1-d7, q 21 days	500 d1-d5, q 28 days	155
SWOG	300/day, d1-d28 q 35 days + LV 20 IV q7 days	425 +LV 20, d1-d5 q28 x 2, then q 35 days	175

Efficacy			
Response	22%	14%	OR= 0.55 (95% CI=0.41-0.75)
Duration of Response	7.1 months	6.7 months	
Survival[a]	12.1 months	11.3 months	HR=0.88 p=0.04

Toxicity			
Gr 3+4 hematologic	4%	31%	P<10^{-16}
Hand-foot syndrome	34%	13%	P<10^{-7}
Other non-heme	14%	13%	--

[a] overall survival were similar in 5-FU CIVI vs 5-FU bolus, that were modulated by LV.

In this meta-analysis, the administration of 5-FU by CI showed a statistically significant increase in survival duration in favor of the 5-FU CIVI schedules (p=0.04). However, the magnitude of benefit was small and a subset analysis of the studies involving modulation by leucovorin did not show significant differences. In contrast, the difference in response rates were highly statistically significant.

> ***Reviewer's comment***: *This study shows response rate and survival data do not always correlate because despite a very significant difference in response rates, there seems to be lack of an equally strong evidence for a survival advantage with infusional 5-FU regimens compared to bolus 5-FU. The hematologic toxicity profile favors infusional 5-FU.*
> *There are two important major points regarding the choice of the control arms for the pivotal trials in this application:*

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[8] The Meta-analysis Group in Cancer. Efficacy of intravenous continuous ifusiopn of fluorouracil compared with bolus administration in advanced colorectal cancer. J Clin Oncol, vol 16, January 1998, pp 301-308

- *For study 0038, there seems to be a convincing argument that the difference in efficacy is seen with the combination of CPT-11 + 5-FU/LV, may be attributed to CPT-11 and not due to a change in the schedule and dosed of 5-FU/LV. The 5-FU/LV schedule in the experimental arm (Arm B) of Study 0038 is similar to the Roswell Park regimen but with a lower weekly dose and dose intensity.*

- Review of the literature comparing infusional with bolus application of 5-FU did not show strong evidence of efficacy in favor of either method of administration.

V. CLINICAL PROTOCOLS

Table 6. Summary of Pivotal Trials

STUDY	T_x ARM	DOSE (mg/m^2)	# OF PATIENTS (ITT)
Study 0038 P&U US, Can, Aus, NZ	**A**: CPT-11 42d course	125 wkly x 4, then 2 wks rest	231
	B: CPT-11/ 5-FU/LV 42d course	125 wkly x 4/ 500/20 wklyx4 then 2 wks rest	226
	C: 5-FU/LV 28d course	425/20 daily x 5	226
V303 RPR Europe, Israel,SA	**A₁**: CPT-11/ 5-FU/LV 7w course	80 wkly x 6 2300 over 24° x 6 500 over 2°	145
	A₂: CPT-11/ 5-FU/LV 6w course	180 on d1 x3w 400-600/22° d1-2 200/2° d1-2 x3w	53 **Total: 198**
	B₁: 5-FU/LV 7w course	2300 over 24° x 6 500 over 2°	143
	B₂: 5-FU/LV 6w course	400 then 600/22° 200/2° x3 w	44 **Total:187**

Study V-303

This is a prospective, non-blinded, randomized, multicenter phase III study comparing CPT-11 plus two infusional schedules of 5-FU/LV (de Gramont and AIT schedules) to the same schedules without CPT-11 in patients with untreated metastatic colorectal cancer.

> ***Reviewer's comment****: This study was undertaken by Phone Poulenc Rhorer (RPR) in Europe and was not registered under the US IND. The original and final versions of the protocol were requested from the sponsor during the pre-NDA meeting and are being reviewed for the first time in this report.*

Title:

A Randomized Phase III Multicenter Trial Comparing Irinotecan Hydrochloride Trihydrate (CPT-11) in Combination with 5 Fluorouracil and Folinic Acid (5-FU/FA) to the Same Schedule of 5 FU/FA in First Line Palliative Chemotherapy in Patients with Metastatic Colorectal Cancer

Participating Countries (v303):

84 centers in 14 countries : Austria, Belgium, Czech Republic, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Spain, South Africa, Sweden, Switzerland, United Kingdom

Study Period (v303):

Start Enrollment: April, 1997
Stop Enrollment Date: December 1997

Reviewer comment*: The planned duration of enrollment was nine months and the planned duration of the study (treatment + follow-up) was 18 months.*

Objectives (v303):

Primary:

"To compare **response rate** after treatment with CPT-11 in combination with 5-FU/FA to response rate after treatment with the same regimen of 5FU/FA in first line in patients with metastatic colorectal cancer."

- An external response review committee (ERRC) consisting of two external radiologists, one physician and one investigator was set up for "blind" assessment of tumor responses.

- The projected response rate is 35% for both regimen of 5FU/FA and 50% for the two corresponding combination regimens. A total of 338 evaluable patients will be needed.
- Response rate will be determined in the intent to treat, eligible and evaluable groups.
- Lesions should be evaluated for response after cycles 2, 4 and 6. Responses should be confirmed after 28 days.
- Determination of Overall Response – bidimensional, unidimensional and evaluable lesions were utilized in the response assessments through tabular algorithms provided in the protocol appendix.

Secondary:

Time to treatment failure
Progression free survival
Overall survival
Quality of life and Other Clinical Benefit Parameters
Safety Profile of Both Arms

Inclusion Criteria (v303):

- Adenocarcinoma of the colon or rectum

- At least one measurable metastatic disease with bidimensionally measureable lesion according to WHO

- No potentially resectable metastases

- 18 to 75 years old

- WHO Performance status #2, life expectancy > 3 months

- Adequate hematological function (Hb$\geq$ 10g/dl, ANC$\geq$2.0 x 10^9, platelets$\geq$150x10^9/L)

- Adequate hepatic and renal function (total bilirubin #1.25 upper normal limits, creatinine <1.25 UNL, AST and ALT <3 ULN) In case of liver metastases, total bilirubin #1.5 x ULN, AST and ALT # 5 xULN.

- No prior chemotherapy or only neoadjuvant chemotherapy ended more than 6 months before randomization

- Time between last antitumor treatment and randomization must be at least **6 months** for adjuvant chemotherapy and **4 weeks** for radiotherapy and surgery

- Able to comply with scheduled follow-up

Exclusion Criteria (v303)

- Pregnant or lactating patients, or those not implementing adequate contraceptive measures during study

- Prior palliative chemotherapy

- Evidence of CNS metastases

- Unresolved bowel obstruction or subobstruction/diarrhea, Crohn's disease or ulcerative colitis

- Chronic diarrhea

- Other serious illness or medical condition

- 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 anticancer or experimental drugs

- Patients clearly intending to withdraw from the study if they are randomized to the willing arm or cannot be followed up

Work-up (v303)

Table 7. Baseline Investigations, Study v303

INVESTIGATIONS	PRE-STUDY SCREEN

History/P.E.
Concomitant Medications
Hematology (CBC, PT/PTT)
  Biochemistry (alk phos, LDH, AST, ALT, creatinine, protein)
  ECG
	# 48 hrs prior to randomization

Tumor Measurements (CEA, CT scans)	#14 days prior to randomization
Quality of Life	#8days after randomization, prior to CPT-11 infusion

Table 8. On Study Investigations, Study v303

INVESTIGATIONS	DURING STUDY
History/P.E. Concomitant Medications	D1 before treatment
Hematology (CBC, PT/PTT)	Weekly
Biochemistry (alk phos, LDH, AST, ALT, creatinine, protein) Assessment of ADR's	Before treatment Arm A: weekly Arm B: biweekly
Tumor Measurements: CT scans ECG	After each cycle (q 6-7 weeks)
Quality of Life	every 6 to 7 weeks, before each cycle treatment

- q 3 months follow-up until death or cut-off date.
- Treatment related side effects followed until resolution.

Study Treatment (v303)

A panel of experts and investigators decided that the regimens above were the two most promising schedules based on impressive Phase 1 data and patterns of use. The DeGramont regimen is being used more in France while the weekly schedule (AIT regimen) is more popular in Germany.

<u>Arm A</u>: CPT-11 Containing/Experimental Arms

<u>Regimen A$_1$</u> (AIO + CPT-11): One cycle represents 6 infusions (7 weeks)

- **CPT-11**, 80 mg/m^2 , 90-minute iv weekly x 6wks on D1,8,15,22, 29, 36

- **Folinic Acid** 500 mg/m^2 over 2 hrs followed immediately by

- **5-FU** 2300 mg/m^2 i.v. over 24 hrs x 6 wks on D1,8,15,22,29 and 36

<u>Regimen A2</u> (DeGramont + CPT-11): One cycle represents 3 infusions (6 weeks) Treatments will be administered every 2 weeks

- **CPT-11**, 180 mg/m^2 ,90-minute iv on D1

- **Folinic Acid** 200 mg/m^2 over 2 hours followed immediately by

- **5-FU** 400 mg/m^2 i.v. bolus and 600 mg/m^2 over 22 hours on D1 and D2

<u>Arm B</u>: Control Arms

<u>Regimen B1</u> (AIO) : Same as regimen A1 without CPT-11

- **Folinic Acid** 500 mg/m^2 over 2 hrs followed immediately by

- **5-FU** 2300 mg/m^2 i.v. over 24 hrs x 6 wks on day 1,8,15,22,29 and 36

<u>Regimen B2</u> (DeGramont): Same as regimen A2 without CPT-11

- **Folinic Acid** 200 mg/m^2 over 2 hrs followed immediately by

- **5-FU** 400 mg/m^2 i.v. bolus and 600 mg/m^2 over 22 hrs on D1 and D2

Table 9. *Treatment and Dose Modification for Arm A, Study v303*

If, at the time of any infusion	Date of Infusion	Dose of Further Infusions
ANC<1.0x10^9/L Plt<75x10^9/L Diarrhea NCI Gr>1 Mucositis NCI Gr >1	• ***Infusion Delayed*** *until ANC $1, plt >75, Diarrhea=Gr. 0, Mucisotos=Gr. 0*	• ***Full Dose*** • ***Reduce Dose by 20% if delayed for > 1 wk***
ANC #0.5x10^9/L ANC# 1.0+fever/Infection Plt<25x10^9/L Diarrhea Gr 3 or 4 Mucositis NCI Gr 3 or 4	When recovery of: ANC$1.0 x10^9/L Plt$75x10^9/L Diarrhea NCI Gr#1 Mucositis NCI Gr #1	***Reduced Dose (-20%)*** Arm A: 5 FU 1850 mg/m^2 CPT-11 65 mg/m^2 Arm B: 5 FU 2000 mg/m^2

Table 10. *Treatment and Dose Modification for Arm B, Study v303*

If, at the time of any infusion	Date of Infusion	Dose of Further Infusions
ANC<1.5x10^9/L Plt<75x10^9/L Diarrhea NCI Gr>1 Mucositis NCI Gr >1	***Infusion Delayed $ one week until recovery ANC $1.5, plt >75, Diarrhea=Gr. 0, Mucositis=Gr. 0***	***Full Dose***

ANC #0.5x10^9/L
ANC# 1.0+fever/Infection
Plt<20x10^9/L
Diarrhea Gr 3 or 4
Mucositis NCI Gr 3 or 4
	When recovery of:
	
	ANC$1.5 x10^9/L
	Plt$75x10^9/L
	Diarrhea Gr#1
	Mucositis Gr #1
		Reduced Dose (-20%)
		
		Arm A:
		5 FU 320 mg/m^2/d (bolus)
		    480 mg/m^2/d (22 h)
		    CPT-11: 150 mg/m^2
		
		Arm B:
		  5 FU 320 mg/m^2/d (bolus)
		    480 mg/m^2/d (22 h)

Reviewer's comment: Note that both the dose of 5-FU and CPT-11 are decreased simultaneously for hematologic toxicities, mucositis and diarrhea, with the exception of hand-foot and mouth syndrome.

Table 11. Concomitant Treatments, Study v303

Atropine	• 0. 25 mg sc for acute severe cholinergic symptoms • no preventive treatment but may be given as prophylaxis if early diarrhea was severe during the prior 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
Fluoroquinolone	• Orally for 7 days for (1) Grade 4 diarrhea; (2) diarrhea for > 48 hours despite recommended loperamide treatment; (3) Diarrhea + Grade 3 neutropenic fever
G-CSF/GM-CSF	• not recommended but may be considered according to guidelines

Treatment Discontinuation
- Toxicity
- Disease progression
- Withdrawal of consent

Follow-up
- Every 6 to 7 weeks while on treatment
- Every 3 months after treatment until death or cut-off date

Protocol Definition of Efficacy Endpoints

1. **Survival**- from randomization to death

2. **Period of Complete Response**- from the date the complete response was achieved to the date thereafter on which progressive disease is first noted.

3. **Period of Overall Response**- from the first day of treatment to the date of first observation of progressive disease.

4. **Progression Free Survival** – the time measured from the day of randomization to the first progression or death

5. **Time to Treatment Failure**- the time measured from the day of the first infusion to the date of failure (progression, relapse, death, withdrawal due to toxicity, patient's refusal or lost to follow-up)

Statistical Plan

- The response rate was projected to be equal to 35% for both regimen of 5FU/FA and 50% for the two corresponding combination regimens. A total of 338 evaluable patients needed to show a significant difference. Response rate was determined in the intent to treat, eligible and evaluable groups.
- The progression free survival was assumed to be 6 months in the 5FU/FA group and 9 months in the CPT-11 + 5FU/FA group. A total of 286 evaluable patients was needed to show a significant difference.
- Standard analyses was performed in the intent-to-treat population. Additional analyses will be performed in the eligible (no major inclusion violations) and evaluable (assessable for response) population.
- Chi^2 Test for categorical variables
- Student's test for continuous variables
- Kaplan Meier method and logrank test for censored data, stratified logrank for subgroups in case of heterogeneity between groups
    > ***Reviewer's comment:*** *The prospectively defined statistical analysis plan was to compare pooled results between Arm A ($A_1 + A_2$) to Arm B ($B_1 +$*

B_2). The number of patients enrolled in each subgroup does not lend enough power to perform independent subset analyses.

Results

Patient Disposition

Table 12. Disposition of Patients, v303

No. of Patients	Arm A: CPT+5FU/LV N (%)	Arm B: 5FU/LV N (%)
Randomized	199 (100)	188 (100)
Full Analysis[a]	198 (99.5)	187 (99.5)
Treated Patients According to Actual Treatment Received [b]	199 (100)	186 (100)
Regimen A_1	54 (27)	--
Regimen A_2	145 (73)	--
Regimen B_1	--	43 (23)
Regimen B_2	--	143 (77)
Per Protocol[c]	169 (85)	169 (90)

[b] one patient was randomized to Arm B but treated with arm A

Definition of Populations

The following populations were defined during the preparation of the study report:
1. [a]Full Analysis Population: All treated patients analyzed in the arm to which they were assigned by randomization. One patient in each arm did not receive study treatment.
   - There was equal distribution among patients who were found to be ineligible post randomization by the ERRC: 14 patients (7%) in Arm A: CPT+5FU/LV and 11 patients (6%) in Arm B: 5FU/LV, mostly due to non-bidimensionally measurable lesions and non-metastatic disease.
2. [c]Per Protocol Population: A subset of the full analysis population who were treated, evaluable for response, and without any major protocol deviations during the study.

> *Reviewer's comment: Assessments of efficacy and safety endpoints were done by the sponsor on both the full analysis and the per protocol*

populations. Unless specified otherwise, only results from the full analysis population (sponsor's results, FDA reviewer's analyses and comparisons) will be presented in this review since it in essence the "Intent to Treat" population.

	Arm A: CPT+5FU/LV N=199	Arm B: 5FU/LV N=186
	N (%)	N (%)
Still on study	25(12.6)	9 (5)
Progressive disease	87 (44)	129 (69)
Consent withdrawn, refused treatment	39 (20)	19 (10)
Other Reasons	17 (8)	14 (8)
Toxicity	18 (8)	5 (3)
Surgery	5 (2)	3 (2)
Death		
Progressive Disease	5 (2)	-
Toxicity	1 (0.5)	2 (1)
Other Reasons	1 (0.5)	1 (0.5)

(NDA 20-571, Vol.3, p.101)

Reviewer's comment*: Since CPT-11 (and other agents) may be available for patients who were treated in Arm B: 5FU/LV, one concern would be a lower threshold for declaring progression of disease compared to patients in Arm A: CPT+5FU/LV who were treated with the combination regimen. Note that there were approximately twice the numbers of patients who withdrew consent and discontinued due to toxicity in Arm A: CPT+5FU/LV. Among others, diarrhea and asthenia were the most common toxicities leading to discontinuation.*

A patient may be withdrawn from treatment for multiple reasons. The distribution by regimen is listed below; however, due to the small numbers, only those >5% are shown.

Table 13 FDA Analysis of Treatment Discontinuation due to Toxicity by Regimen (v303)

	Regimen			
	A_1 (weekly) N=54	A_2 (biweekly) N=145	B_1 (weekly) N=43	B_2 (biweekly) N=143
Toxicity	**9 (17%)**	**9 (6%)**	**4 (9%)**	**1 (1%)**
Diarrhea	5 (9)	4 (3)	2 (5)	--
Vomiting	3 (6)	--	1 (2)	--
Neurologic Symptoms	5 (6)	1 (1)	--	--

Treatment discontinuations due to toxicity in the CPT-11 containing regimens in Arm A: CPT+5FU/LV are more than twice the number in the non-CPT-11 containing regimens. There were three times more treatment discontinuations in Regimen A_1 compared to A_2.

Patient Demographics

Table 14. Pretreatment Characteristics, v303

Treatment Arm	Arm A: CPT+5FU/LV		Arm B: 5FU/LV	
	N	%	N	%
Number of Patients	198	100	187	100
Male/Female (%)	132/66	**67/33**	99/88	**53/47**
			p = 0.006	
WHO Performance Status				
0	102	52	96	51
1	83	42	77	41
2	13	7	14	8
Primary Tumor Location				
Colon Right	43	22	39	21
Colon Left	64	32	80	43
Colon Right and Left	1	1	2	1
Rectum	80	**40**	60	**32**
Rectosigmoid	10	**5**	6	**3**
			p =0.0042	
Number of Organs Involved				
1	123	62	117	63
2	46	23	53	28
3	25	13	14	8
>3	4	2	3	2
Sites of Disease				
Liver	152	77	149	80
Liver alone	89	45	93	50
Liver + Other sites	63	32	56	30
Lung	52	26	43	23
Lymph Nodes	28	14	24	13
Peritoneum/ Retroperitoneum	20	10	22	12

(summarized from Final Study Report, v303, vol 1 p.204-205)

There were statistically significant differences between gender and the number of patients with rectal + rectosigmoid tumors between the treatment arms.

> *Reviewer's comment: The imbalance in the number of patients with rectal and rectosigmoid tumors in favor of CPT-11 was a concern. A stratified*

*analysis of survival according to site of primary tumor (colon vs. rectum)
by the sponsor did not show a significant difference in survival based on
the location of the primary lesion. The median survival of patients with
rectal tumors in Arm A:CPT-11+5-FU/LV (N=80/198) was 18.3 months
(95%CI 15.6-21.5) vs. Arm B:5-FU/LV, (N=60/187) 17.4 months
(95%CI=13.1-19.2).*

The following table summarizes prior anticancer treatments received by patients:

Table 15. Prior Anticancer Therapy (v303)

	Arm A: CPT+5FU/LV (N=198)		Arm B: 5FU/LV (N=187)	
	N	%	N	%
Adjuvant Chemotherapy	51	26	44	24
Surgery	176	**89**	177	**95**
Radiotherapy	40	20	29	16

There were significantly more patients in Arm B: 5FU/LV who had prior surgery but more patients in Arm A: CPT+5FU/LV who had prior radiation therapy.

Efficacy (v303)

The following table contains the protocol defined analyses of the study endpoints. The analyses performed in the study report are listed on the third column.

Table 16. Summary of Protocol Defined vs. Actual Anlayses Performed (v303)

ENDPOINT	PROTOCOL DEFINITION	ACTUAL ANALYSES PERFORMED
Response Rate	• Blinded Assessment by the ERRC • Calculated on ITT, Evaluable and Eligible populations	• Done According to Protocol Definitions
Duration of Response	• first infusion to PD or death	• first infusion to first documentation of PD
Time to Onset of First Response	• Not defined	• first infusion to response
Time to Progression	• Randomization to PD • ITT Population	• Done According to Protocol Definitions
Time to Treatment Failure	• randomization to PD or treatment discontinuation	• Done According to Protocol Definitions
Progression free survival	• randomization to PD • ITT Population	• Done According to Protocol Definitions
Survival	• randomization to death	• Done According to Protocol Definitions • analysis on an intent-to-treat basis • Kaplan-Meier estimates • stratified logrank tests[a] with <u>retrospective</u> stratification of prognostic factors
Quality of Life	• comparison of PS and symptom evolution • Time to onset of symptom • Comparison of the results of the EORTC QLQ-C30	• Analgesic consumption • Time to Deterioration of PS • Time to definitive weight loss • Time to pain appearance in pain free patients at baseline

- The clinical cut-off date was planned to be **October 15, 1998** in order to allow for the last included patient to have at least 6 months on study. This was changed to **November 26, 1998** in order to be able to assess the time to progression of the DeGramont regimen with a power of 0.8 (needed 197 events). The cut-off date for survival was **February 2, 1999.**

- Efficacy results were determined both by the investigator and the Expert Review Committee (ERRC)

Survival (Secondary Endpoint) V303

- Enrollment occurred between May 1997 and February 1998. The original cut-off date for the analysis of survival was pre-specified on February 8, 1999 at which time 60% of patients in Arm A: CPT+5FU/LV and 49% in Arm B: 5FU/LV were still alive. The median overall survival of all randomized patients was significantly longer in Arm A: CPT+5FU/LV: 16.8 months versus 14 months in Arm B:5-FU/LV with a p value =0.028.

**Table 17. Sponsor Analysis of Survival (ITT)
Study V303 (Cut-off Date Feb. 1999)**

Arm	No. of Pts.	No. of Failures (%)	Survival (months)		p-value
			Median	Range	
A	198	80 (40)	16.8	0.4-19.9	**0.028**
B	187	96 (51)	14	1.5-19.4	

Survival

Tests			
Test	Chi-Square	DF	Prob>ChiSq
Log Rank			
Wilcoxon			
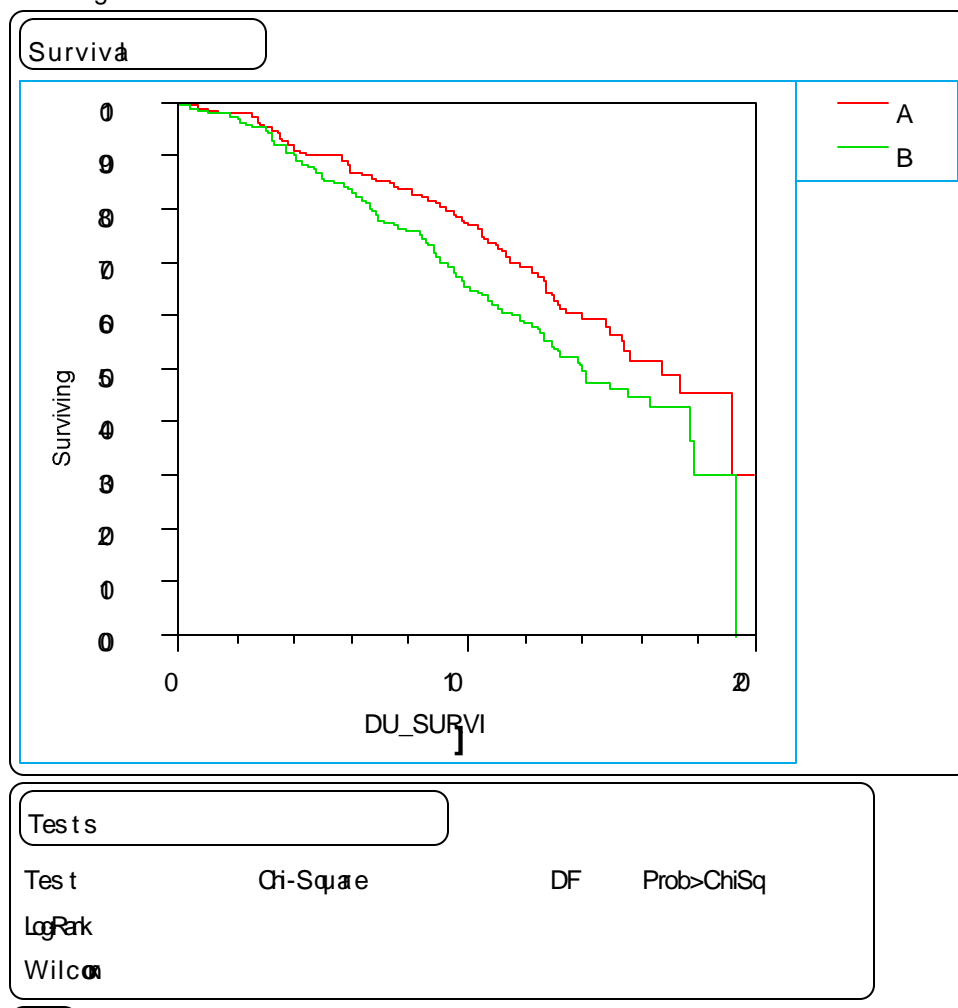
Reviewer's comment: *The sponsor's survival curve was verified using the JMP program on primary data submitted. The median survival for Arm A: CPT+5FU/LV was 16.7 months and Arm B: 5FU/LV was 14 months with significant difference in favor of Arm A: CPT+5FU/LV (p=0.028).*

The FDA requested additional survival data on December, 1999. The updated data submitted by the sponsor had a new cut-off date of October 27, 1999.

**Table 18. Sponsor Analysis of Survival (ITT)
Study V303 (Cut-off Date Oct. 1999)**

Arm	No. of Pts.	No. of Failures (%)	Survival (months)		p-value
			Median	Range	**0.032**
A	198	126 (64)	17.4	0.4-28.3+	
B	187	136 (73)	14.1	0.5-27.6+	**HR=0.77 (0.6-0.98)**

Reviewer's comment: This update was requested by the FDA in order to capture the latest available data and establish a more mature survival curve. These results confirm the conclusion of a significant survival advantage in favor of CPT-11 +5-FU/LV.

Display 4. Survival – Kaplan-Meier Estimates
(Study V303 Full-Analysis Population)

p=.032 (log-rank)

—Irinotecan/5-FU/LV (N=198)
— 5-FU/LV (N=187)
▲ Censored
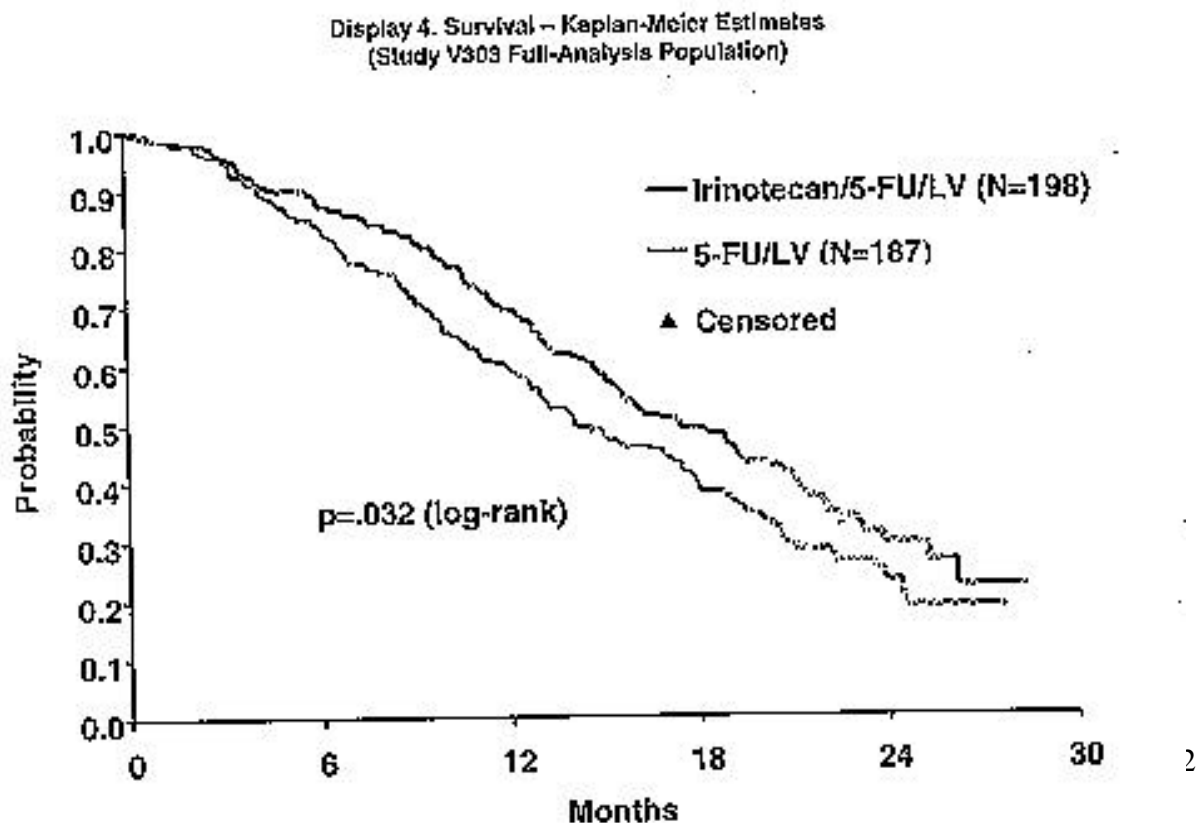
Table 19 Stratified Analysis of Survival According to Baseline Patient Characteristics (V303)

Prognostic Factor	Arm A: CPT+5FU/LV		Arm B: 5FU/LV	
	Median	95%CI	Median	95%CI
Age				
<65	16.8	15.0-20.7	13.3	11.1-17.4
$65	18.2	12.8-21.3	15.4	12.7-20.0
Performance Status				
0	25.3	20.7-NE	17.1	13.3-20.0
>0	13.0	11.1-14.8	13	9.9-15.0
Site of Primary Tumor				
Colon	15.8	13.0-20.7	13.2	11.9-16.9
Rectum	18.3	15.6-21.5	17.4	13.1-19.2
No. Of Organ Sites				
1	18.8	15.4-21.5	16.9	13.0-19.4
2	17.7	12.8-22.0	14.1	10.7-17.4
>2	12.8	9.7-19.3	9.1	5.1-11.6
Liver Involvement				
No	19.2	14.0-NE	15.0	11.2-24.4
Yes	16.8	14.7-20.7	13.9	12.3-17.7
Prior Adjuvant 5-FU				
No	16.1	14.7-20.1	14.1	12.1-17.7
Yes	19.3	14.8-21.5	14.9	11.2-20.5
Serum LDH				
# ULN	20.7	17.3-NE	17.9	14.1-20.7
>ULN	14.7	11.0-18.2	11.1	8.9-14.6
Hemoglobin				
<11 g/dl	14.0	12.5-18.8	10.2	9.1-13.9
$11 g/dl	18.8	15.6-21.2	15.5	13.0-18.0

Reviewer's comment: It may be observed that certain patient characteristics which may be related to low tumor burden such as good performance status, normal serum LDH, a low number of involved organs and normal bilirubin, may be favorable predictive factors for improved survival.

- Further treatment with antitumor therapy: 41% in Arm A: CPT+5FU/LV and 59% in Arm B: 5FU/LV received additional chemotherapy. In Arm B: 5FU/LV, 31% received a CPT-11 regimen and 12% received an Oxaliplatin-containing regimen. For patients in Arm A: CPT+5FU/LV, 16% received an Oxaliplatin-containing regimen.

> *Reviewer's comment: Interpretation of the survival endpoint data may be problematic with extensive crossover to active drugs such a CPT-11and oxaliplatin.*
>
> *A statistically significant survival advantage shown for patients who were treated in Arm A: CPT+5FU/LV despite crossover by patients from Arm B: 5FU/LV to CPT-11 containing regimens indicate that the effect of first-line treatment with CPT-11 on survival is present, and an even greater survival benefit may have been obliterated. The two arms are reasonably balanced for other treatment agents such as oxaliplatin. It seems unlikely that other therapy given after CPT-11 could be responsible for the observed survival benefit.*

Response Rate (Primary Efficacy Endpoint)

- The projected response rate is 35% for both regimen of 5FU/FA and 50% for the two corresponding combination regimens. A total of 338 evaluable patients was be needed to show a significant difference. Response rate was be determined in the intent to treat, eligible and evaluable groups.
- An external response review committee (ERRC) consisting of two external radiologists, one physician and one investigator was set up for "blind" assessment of tumor responses.

- Only 369 out of the 385 patients of the full analysis population were evaluated by the ERRC for objective tumor response, 193 (97%) in Arm A: CPT+5FU/LV and 176 (94%) in Arm B: 5FU/LV. For 16 patients who were not evaluated, (5 in Arm A: CPT+5FU/LV and 11 in Arm B: 5FU/LV) the investigator's assessment of tumor response was taken into account.

The following table summarizes the discrepancies between investigator and ERRC assessment of tumor response status:

Table 20. FDA Summary of Discrepancies Between the Investigator and the ERRC Assessments of Tumor Response

Downgraded			Upgraded			(Upgraded) – (Downgraded)/	
	Arm A: CPT+5FU/LV	Arm B: 5FU/LV		Arm A: CPT+5FU/LV	Arm B: 5FU/LV	Arm A: CPT+5FU/LV	Arm B: 5FU/LV
CR→PR	3	2	PR→CR	4	--	+1	-2
CR→NC	1	--	NC→CR	--	--	-1	0
PR→NC	14	12	NC→PR	15	7	+1	-5
PR→PD	1	1	PD→PR	2	--	+1	-1
NC→PD	12	11	PD→NC	5	10	-7	-1

> *Reviewer's comment: Best overall response rate was improved in Arm A: CPT+5FU/LV, with the addition of 2 responses. There was a net of 8 downgrades in Arm B: 5FU/LV. The number of CR's in Arm A: CPT+5FU/LV were unchanged; however, the two CR's in Arm B: 5FU/LV were downgraded.*
>
> *The assessment made by the ERRC improved the results for Arm A: CPT+5FU/LV and increased the difference in response rates between the treatment arms compared to the investigators assessments.*

According to the ERRC, the following patients were non-evaluable for response:

Table 21. Reasons for Non-Evaluability for Response (v 303)

	Arm A: CPT+5FU/LV N=199 (%)	Arm B: 5FU/LV N=188 (%)
Early Discontinuation for toxicity/ Patient refusal	9 (4.5)	2 (1.1)
Response not properly assessed	6 (3)	3 (1.6)
Other	6 (3)	6 (3.2)
Total No. of non-evaluable patients	21 (11)	11 (6)

Reviewer's comment: Having more non-evaluable patients puts Arm A: CPT+5FU/LV at a relative disadvantage for response analysis.

Table 22. Overall Response Rate (Full Analysis Population) v 303

	Arm A: CPT+5FU/LV (N=198)		Arm B: 5FU/LV (N=187)	
	N	%	N	%
CR	6	3	--	--
PR	63	32	41	22
Overall Response Rate	69	**35**	41	**22**
95% C.I.	(28.2-41.9)		(16.2-28.5)	
p-value (Chi Square)	<0.005			

Reviewer's comment: The overall response rate for Arm A: CPT+5FU/LV was lower than predicted (50%); nevertheless, it was still significantly superior compared to the response rate in Arm B: 5FU/LV.

Duration of Response

- The median duration of response was 9.3 months (2.8-13.1) in Arm A: CPT+5FU/LV and 8.8 months (3.7-11.8) in Arm B: 5FU/LV. This difference was not statistically significant. (p=0.08)

    Reviewer's comment: There was heavy censoring among patients in Arm A: CPT+5FU/LV (40 of the 69 responders, 58%) and Arm B: 5FU/LV (17/41, 41%); the most common reasons being "no documentation of progression" and "event occurring after the cut-off date".

Time to Progression

- The median time to progression in the full analysis population was significantly longer in Arm A: CPT+5FU/LV (6.7 months) vs. Arm B: 5FU/LV (4.4 months) with a p value <0.001

- The main reason for censoring was "no event before cut-off date" for 33% of patients in Arm A: CPT+5FU/LV and "further chemotherapy" in Arm B: 5FU/LV (44%)

    Reviewer's comment: There were a significant numbers of patients "censored" and not counted as "events" because of receiving further chemotherapy without documentation of progression. There is no good

way to deal with this problem. Counting such events as progression would underestimate the time of progression, while censoring them would overestimate it. One approach is to evaluate the robustness of this finding by doing the analysis both ways. If the Camptosar arm is superior by both analyses, then the results are likely to be reliable. The analysis of time to treatment failure is probably a good sensitivity test for the time to progression analysis since it counts all such events as failures.

Time to Treatment Failure

- Calculated from date of randomization until disease progression or treatment discontinuation
- The median time to treatment failure was significantly longer in Arm A: CPT+5FU/LV   compared to Arm B: 5FU/LV: 5.3 months (0.4-15.7) versus 3.8 months (0.4- 11.5+), respectively (p=0.0014)

> ***Reviewer's comment:***. *The highly significant result in favor of the CPT-11 +5-FU/LV establishes the robustness of the findings in time to tumor progression.*

Sponsor's Retrospective Analyses of Clinical Benefit

Identification and analysis of specific clinical benefit endpoints shown in the following table was done retrospectively:

Table 23. Summary of Retrospectively Defined Clinical Benefit Endpoints, v303

	Arm A: CPT+5FU/LV	Arm B: 5FU/LV	p-value
Time to PS Deterioration in Patients with PS Evaluation at Baseline	11.2 months (0.1-15.7+)	9.9 months (0+-13.6+)	**0.046**
Time to Weight Loss >5% in Patients with Weight Loss Evaluation at Baseline	Median not reached	11.2 months	**?**

Appearance of Pain in Pain-free Patients at Baseline	4 patients (3%)	6 Patients (5%)	?
Opioid Consumption Cycle 1 Cycle 2 Cycle 3 Cycle 4	52 (26%) 23 (14%) 11 (8%) 8 (7%)	48 (27%) 29 (20%) 22 (20%) 12 (16%)	

Reviewer's comment: Time to PS Deterioration
Although good performance status is a covariate that predicts for good response and less toxicity from treatment, the clinical significance of "deterioration of performance status" is unclear in the setting of first-line treatment of colon cancer where a majority of patients who enter the study have good status. A deterioration in the performance status may be due to several factors not be related to toxicity or efficacy of treatment. Furthermonre, one "significant" finding among several retrospective analyses suggests that this is as interesting exploratory finding, rather than a statistically significant one.

Reviewer's comment: Time to Definitive Weight Loss >5%
Change in weight may or may not be a true indication of clinical benefit. Since major fluid losses secondary to treatment side effects may occur, a 5% change may not be sensitive enough to detect a clinically meaningful change in weight. There were more patients who reported loss of weight in Arm A: CPT+5FU/LV (n=17, 8%) versus patients in Arm B: 5FU/LV (n=8, 4%).

Reviewer's Comment: Analgesic Consumption
No firm conclusions can be made regarding analgesic consumption due to the retrospective nature of data collection.

Summary of Efficacy Results By Regimen

The following table presents results from individual regimens in each treatment arm in Study v303:

Table 24. Summary of Efficacy Results by Regimen

	Arm A: CPT+5FU/LV		Arm B: 5FU/LV	
	A1 (AIO+ CPT-11)	A2 (deGramont +CPT-11)	B1 (AIO)	B2 (deGramont)
Number of Patients (%)	54(100)	145 (100)	43(100)	143 (100)
Overall Response (%)	21 (40)	48(33)	11 (25)	30(21)
Duration of Response (months)	8.9	9.3	6.7	9.5
Time to Progression (months)	7.2	**6.5**	6.5	**3.7**
Time to Treatment Failure (months)	5.4	**5.1**	5.0	**3.0**
Overall Survival (months)	19.2	**15.6**	14.1	**13**

> ***Reviewer's comment***: *Analysis of efficacy from the two major treatment subsets suggests that CPT-11 contributes to the efficacy of each group. However, statistically significant findings regarding the benefit of adding CPT-11 to the AIO regimen are not documented perhaps because there were only 50 paitients per arm in this comparison. Approximately 75% of the patients received the DeGramont regimen (A2 and B2) and results of the efficacy analyses are shown above, (statistically significant differences (i.e. p#0.05) are written in bold). Exploration of the efficacy results from*

the treatment subsets support the efficacy conclusions from the pooled analysis.

Safety (v303)

PROTOCOL DEFINITION	ACTUAL ANALYSES PERFORMED
• Safety will be compared in the two treatment arms	• Analysis performed on overall and by regimen on population evaluable for safety
• Safety evaluation by patient and by cycle	• Tabulations of maximum NCI grade and severity by patient and by cycle
• Adverse events reported using the NCI CTC	• *Grade 3-4 adverse events compared between treatment groups*
• Compare incidence, severity and seriousness of AE	• *Defined specific laboratory results to be compared: leukopenia, neutropenia, anemia and thrombocytopenia, creatinine, alk phos, SGOT, SGPT. Total bilirubin*
	• *Duration of Gr 3-4 neutropenia and time to recovery were analyzed*
	• *Serious adverse events analyzed by patient*
	• *Hospitalizations*
	• *Deaths within 30 days and after 30 days from last infusion*

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

Reviewer's comment: The following table shows the frequency of adverse events in the study as reported by the sponsor (rounded to the nearest whole number). Only toxicities with an incidence of >10% are shown. Fisher's exact test by the FDA shows those with significant differences, p<0.05 .

Table 25. Sponsor's Summary of Toxicity, v303

	ARM A: CPT+5FU/LV (N=199) (N/%)		ARM B: 5FU/LV (N=186) (N/%)		Fisher's Exact Test	
	Total (%)	Gr3/4 (%)	Total (%)	Gr3/4 (%)	p-value (total)	p-value Gr.3/4
Diarrhea	153 (77)	45 (23)	93 (50)	20 (11)	**<.0001**	**0.0026**
Nausea	138 (70)	7 (4)	107 (58)	7 (4)	**.020**	
Pain	122 (61)	18 (9)	109 (59)	17 (9)		
Asthenia	111 (56)	19 (10)	81 (44)	6 (3)	**.019**	**.013**
Alopecia	102 (51)	-	31 (17)		**<.0001**	
Vomiting	95 (48)	11 (6)	69 (37)	6 (3)	**.0023**	.326
Mucositis	72 (36)	6 (3)	56 (30)	5 (3)		
Anorexia	70 (35)	7 (4)	40 (22)	2 (1)		
Infection w/o Grade 3 or 4 Neutropenia	69 (35)	12 (6)	59 (32)	6 (3)		
Constipation	60 (30)	1 (<1)	46 (25)	3 (2)		
Cholinergic Symptoms	52 (26)	3 (2)	1 (<1)	--	**<.0001**	.249
Neuromood	46 (23)	5 (2)	32 (17)	2 (1)		
Abdominal Pain	43 (22)	6 (3)	28 (15)	2 (1)		
Fever	42 (21)	1 (<1)	45 (24)	2 (1)		
Lung	36 (18)	3 (2)	20 (11)	1 (<1)		
Hemorrhage	24 (17)	5 (3)	19 (10)	1 (<1)		
Cutaneous Signs	33 (17)	1 (<1)	37 (20)	--		
Thrombosis	31 (16)	8 (4)	17 (9)	1 (<1)	.064	**.038**
Hand and Foot Syndrome	24 (12)	1 (<1)	35 (19)	3 (2)	.089	.357
Cardiovascular Disorders	22 (11)	11 (6)	11 (6)	1 (<1)	.10	**.0059**

(Final Study Report, v303, vol. 1, p. 253)

Death within 30 Days of Treatment (Arm A)

A total of eight patients died (8/198, 4%) within 30 days of last treatment in the CPT-11 arm and six patients (6/187, 3%) in the control arm.

> *Reviewer's comment: According to the sponsor's assessment of patients in Arm A, six patients died from progressive disease, one from heart failure and one from treatment related adverse events. Of the six patients who died in Arm B, four patients died from disease progression, one from myocardial infarction, and one from massive GI bleeding.*
>
> *After reviewing the patient narratives, the FDA reviewer believes that five of the six patients whose death were labeled as " from progressive disease" in Arm A may have treatment related toxicity that may have contributed to the patients' demise (5 of 198, 2%). The reviewer agrees with the assessment of patient deaths in the control arm (Arm B).*

Figure 1. FDA Reviewer's Summary of Benefits, Risks and Concerns,
Study v303

BENEFITS/ STRENGTHS	**RISKS/ WEAKNESSES**	**CONCERNS/ UNCERTAINTIES**

Study Design and Conduct

- Large, randomized, well-controlled
- Independent monitoring committee
- Prognostic factors well-balanced between treatment arms

Efficacy

BENEFITS/ STRENGTHS	**RISKS/ WEAKNESSES**	**CONCERNS/ UNCERTAINTIES**
• Well-controlled and appropriate censoring for survival • Statistically significant and consistent survival advantage favoring CPT-11 • Statistically significant differences in TTP, response rate favoring CPT-11 • Consistent efficacy in favor of CPT-11 • ERRC (third party) confirmation of response, TTP and TTF assessments	• Whether to recommend one or both 5-FU/LV combination regimens	• Impact of subsequent chemotherapy received by patients in either arm • Less data collected with the AIO regimen

BENEFITS/ STRENGTHS	RISKS/ WEAKNESSES	CONCERNS/ UNCERTAINTIES

Quality of Life

   (to follow)

Analyses of Weight, PS and Analgesic Use

- Exploratory, retrospective analyses
- Uncertain clinical relevance of established parameters

Safety

-

- Significantly more nausea, vomiting, cholinergic symptoms, alopecia
- Significantly more severe diarrhea
- 4% early deaths, 5 of 8 deaths probably related to treatment

Study 6475/0038

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/Coordinating Investigator:

Leonard B. Saltz, MD
Memorial Sloan-Kettering Cancer Center
New York, NY

Study Centers (0038):

71 centers in the following countries: United States: 49, Canada: 11, Australia: 8, New Zealand: 3, etc.

Study Design (0038)

This is a multicenter, open label, randomized and controlled three arm trial comparing the safety and efficacy of CPT-11 alone (Arm A: CPT) versus the combination of CPT-11 and 5-FU/Leucovorin, (Arm B: CPT-11+ 5FU/LV) versus 5-FU/Leucovorin alone (Arm C). This study is on patients with previously untreated metastatic colorectal cancer or disease-free for $12 months following adjuvant 5-FU based therapy.

Objectives (0038)

"To compare the efficacy and safety of CPT-11 alone, an investigational combination of CPT-11 and 5-FU/LV, and a standard regimen of 5-FU/LV in patients with metastatic colorectal cancer who have not received any prior therapy or radiation therapy for the treatment of colorectal cancer."

> ***Reviewer's comment:*** *The protocol was amended on May 1998 (date of original protocol: May 1996) to state that the overall objective of the trial was to compare Arm B: CPT-11 5FU/LV with Arm C:5-FU/LV; and Arm A: CPT-11 was included to "document the activity and safety associated with the first-line use of single agent irinotecan in a large multicenter study".*
>
> *The sponsor submitted the planned statistical analysis of this study on December, 1997. The FDA statistician noted the need for adjustment for multiple endpoint comparisons since this was a three-arm study.*

The decision to limit the comparison between two arms in this study was probably done to avoid such adjustment for multiple endpoint comparisons that would have made it more difficult to show statistical significance among the efficacy endpoints at a reduced alpha level.

Endpoints (0038):

Reviewer's comment: The sponsor and the FDA discussed this protocol on May 1, 1996 in the context of using it as the confirmatory Phase 4 trial that would convert the accelerated approval status to full approval status in the treatment of patients with recurrent metastatic colorectal cancer. Parts of the meeting minutes are inserted where appropriate. Endpoints written in italics were added to the original protocol as addenda.

Primary: Time to Tumor Progression

Secondary:

Response Rate
Percentage of Patients whose TTP is $ 6 months
Percentage of Patients who survive $ one year beyond the start of treatment

Reviewer's comment: The Agency noted that <u>survival</u> should be included as a primary endpoint of the study. The sponsor added survival, time to treatment failure and time to response as secondary endpoints added as an amendment to the protocol in May 1998.

Quality of Life

Tertiary:
Weight
Performance status
Tumor related signs and symptoms

Table 26. "Evolution" of Efficacy Endpoints, Study 0038

Original Protocol Defined
1°: Time to Progression
2°: - Response Rate
- %Patients whose TTP is $ 6 months
- %Patients who survive $ one year beyond the start of treatment
3°: Clinical Benefit: weight, PS, tumor related signs and symptoms

---

Original Protocol Defined

1°: Time to Progression

2°: - Response Rate
- %Patients whose TTP is $ 6 months
- %Patients who survive $ one year beyond the start of treatment

3°: Clinical Benefit: weight, PS, tumor related signs and symptoms

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Added as Amendment on Second Year of Study (May 1998)

2°: -Survival
-Time to Response
-Duration of Response
-Time to Treatment Failure

3°: -(Tumor related signs and symptoms-Removed)

Treatment Administration Endpoints
- Total number of courses administered
- Median (range) of courses administered
- Dose modification and delays
- Dose intensity

Added Analyses in Study Report

2° -Probability of Being without Tumor Progression at Six Months
- Probability of Being Without Treatment Failure at 6 Months
- Overall Objective Tumor Response Rate
- Confirmed Objective Tumor Response Rate
- CEA Response Rate

3° - A decline in weight by 5% from baseline
- No worsening of PS by $1 point on the ECOG Scale

Reviewer's comment: Kaplan –Meier curves and log-rank tests which utilize all of the time to event data are more informative than looking at probabilities of events at specific, retrospectively determined time points.

The clinical benefit endpoints evaluating changes in weight and performance status were not defined in the protocol and are presented retrospectively in the study report. The clinical significance of these retrospective analyses is uncertain.

Inclusion Criteria (0038):

- Documented metastatic colorectal carcinoma

- Bidimensionally measurable metastatic disease

- No potentially resectable metastases

- 18 to 75 years old

- ECOG 0 to2, life expectancy > 3 months

- Adequate hematological function (Hb$ 9 g/dl, WBC$3500/mm^3, granulocytes $1500/mm^3 platelets$100x10^9/L)

- Adequate hepatic and renal function (total bilirubin #2.0 mg/dl, creatinine <2.0 mg/dl, AST and ALT <3 ULN) In case of liver metastases, AST and ALT # 5 xULN.

Exclusion Criteria (0038)

- Prior treatment of metastatic disease

- Prior adjuvant 5-FU based therapy and developed recurrence of disease within 12 months of completion of adjuvant therapy

- Prior pelvic radiotherapy

- Pregnant or lactating patients, or those not implementing adequate contraceptive measures during study

- Other serious illness or medical condition

- Past or current history of neoplasm other than colorectal carcinoma, except for cured non melanoma skin cancer or in situ carcinoma of the cervix

- History of myocardial infraction within 6 months or evidence of CHF requiring therapy

- Psychiatric disorders, 5-FU allergy, known brain metastases, active or uncontrolled infection, HIV infections.

- Large pleural effusions or ascites must be drained.

Work-up (0038)

Table 27. Baseline Investigations, Study 0038

INVESTIGATIONS	PRE-STUDY SCREEN
History and P.E. Performance Status CEA Hematology (CBC, PT/PTT) Biochemistry (alk phos, LDH, AST, ALT, creatinine, protein) Baseline QOL	# 7 days prior to treatment
Oncologic History Tumor Measurements (CT, x-ray) EKG Chest X-Ray	#21 days prior to treatment

Table 28. On Study Investigations, Study 0038

INVESTIGATIONS	DURING STUDY
History/P.E. Performance Status Hematology (CBC, PT/PTT) Electrolytes, Chemistries Toxicities Concomitant Medications	Course X, week 1
Toxicities Concomitant Medications Hematology (CBC, PT/PTT)	Course X, week 2,3 4 for Arms A,B Course X, days 2,3,4,5 Arm C And week 2,3,4 for Arm C
Tumor Measurement	At six weeks, 12 weeks, then every 12 weeks. Responses confirmed at 4-6 weeks, then every 12 weeks
CEA Quality of Life	Every 6 weeks

Table 29. End of Study Assessments, Study 0038

INVESTIGATIONS	END OF STUDY
History/P.E. Performance Status Hematology (CBC, PT/PTT) Toxicities CEA Tumor Assessment Quality of Life Treatment Completion Report	
Toxicities Deaths	Until 30 days post treatment. All patients followed until death

Study Treatment (0038)

Table 30. Treatment Arms, Study 0038

	Arm A:CPT-11[a]	Arm B: CPT-11+5-FU/LV[b]	Arm C: 5-FU/LV[c]
Course Duration	42 days	42 days	28 days
CPT-11	125 mg/m^2 weekly x 4, 2 weeks rest	125 mg/m^2 weekly x 4, 2 weeks rest	--
5-FU	--	500 mg/m^2 weekly x 4	425 mg/m^2 daily x 5
Leucovorin	--	20 mg/m^2 weekly x 4	20 mg/m^2 daily x 5

<superscript>a</superscript> Subsequent CPT-11 doses may be adjusted in 25 to 50 mg/m^2 increments
<superscript>b</superscript> Subsequent CPT-11 adjusted in 25 mg/m^2 increments, 5-FU adjusted in 100 mg/m^2 increments
<superscript>c</superscript> Subsequent 5-FU adjusted in 85 mg/m^2 increments

- For DLTs requiring dose reduction, the reduced doses of chemotherapy remained decreased on subsequent treatment courses

- Toxicity on week 4: Omit Week 4, then shorter 5-week course

- Toxicity on Week 2 and/or 3: One of the two weeks rest, break after the completion of three doses in a 6-week treatment course

- After toxicity, conditions allowing retreatment: AGC >1500, platelets> 100K, diarrhea resolved. Same doses given if fully resolved after one week delay, doses reduced by one level if delayed for two weeks, reduced by two levels if delayed for more than two weeks.

Table 31. Concomitant Treatments, Study 0038

Atropine	• 0. 25 mg sc for acute cholinergic symptoms
Loperamide	• 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	• Dexamethasone, 10 mg IV as pretreatment
G-CSF/GM-CSF	• not recommended but may be considered in patients with prior serious neutropenic complications

Treatment Discontinuation

- Toxicity
- Disease progression
- Withdrawal of consent
- Non cancer-related illness preventing therapy or follow-up
- Changes in patient's medical condition that would prevent treatment or follow-up

Protocol Definition of Efficacy Endpoints (0038)

1. **Response Rate** : PR + CR

2. **Time to response:** Randomization to first response

3. **Duration of Response**- first date of response to first note of progressive

4. **Time to Tumor Progression**- Randomization to first note of progressive disease or death in the absence of previous documentation of progressive disease.

5. **Time to Treatment Failure** - Randomization to the date of failure (progression, relapse, death, withdrawal due to toxicity, patient's refusal or lost to follow-up)

6. **Survival**- Randomization to date of death

Statistical Plan (0038)

- Response parameters were performed in the intent-to-treat and evaluable population. Chi square test for comparisons between response rates , multiple logistic model for certain prognostic factors.

- Clinical benefit parameters: tabulated and summarized in frequency tables
  - Patients were categorized by their change in performance status and weight, using both measures of central tendency and comparisons of baseline
  - The duration of stable or improved performance status or weight ($<3\%$ weight loss) were measured

    Reviewer's comment: Measurement of change from baseline at a variety of points raises the problem of multiple comparisons. More importantly, these changes should be defined prospectively and considered clinically meaningful.

Results: Study 0038

The following designations will be used:

Arm B: CPT-11 + 5-FU/LV
Arm C: 5-FU/LV
Arm A: CPT-11

Patient Disposition

Table 32. Disposition of Patients, 0038

No. of Patients	Arm B: CPT-11+ 5-FU/LV	Arm C: 5-FU/LV	Arm A: CPT-11
Randomized (Intent-to Treat)	231	226	226
Never Treated	4	8	4
Received Different Treatment Arm	2	1	1
Treated Patients According to Randomized Treatment	225	217	221

Reviewer's comment: Out of eight patients in Arm C:5-FU/LV who were not treated, four patients withdrew consent.

Definition of Populations

- Intent-to-Treat Population: all patients randomized, with treatment assignment designated according to initial randomization
- Evaluable Population: All patients who correctly receive treatment assigned and meet the eligibility criteria

Randomization Procedure (Study 0038)

Patients were stratified according to four factors: performance status (0 vs 1,2), age (<65 vs. >65), previous treatment (5-FU vs no 5-FU) and time from initial diagnosis (<6 months vs. > 6 months). Patients within each of the sixteen strata were assigned to a random selection of one of the three regimens centrally via an automated telephone/facsimile system.

Patient Demographics

The treatment arms were comparable at baseline in terms of stratification factors of age, performance status, prior adjuvant 5-FU therapy and time from initial diagnosis to study randomization.

There were significantly more males in Arm B: CPT-11+5-FU/LV compared to Arm C: 5-FU/LV. (p=0.019) Gender has not been identified as an important prrognostic factor in this disease. Except for these differences, patient pretreatment characteristics were similar between treatment arms.

Table 33. Pretreatment Characteristics, 0038

Treatment Arm	Arm B: CPT-11+5-FU/LV N=231	Arm C: 5-FU/LV N=226	Arm A:CPT-11 N=226
Median Age (Range)	62(25-85)	61(19-85)	61(30-87)
Male/Female (%)	151/79(**65/34**)	123/101(**54/45**)	145/80(64/35)
	P=0.016		
Performance Status			
0	89 (38)	93 (41)	104 (46)
1	106 (46)	102 (45)	103 (46)
2	35 (15)	29 (13)	18 (8)
Site of 1° Tumor			
Colon	188 (81)	192 (85)	189 (84)
Rectum	38 (16)	31 (14)	33 (15)
Missing	5 (2)	3 (1)	4 (2)
Time from Diagnosis to Randomization			
Median (months)	1.9	1.7	1.8
No. of Involved Organ Sites			
1	147 (64)	149 (66)	140 (62)
2	59 (26)	52 (23)	64 (28)
>2	24 (10)	23 (10)	21 (9)
Liver Involvement			
Yes	189 (82)	185 (82)	188 (83)
No	41 (18)	39 (17)	37 (16)

(summarized from Final Study Report, 0038, vol.11 pp.73-74)

Table 34. Prior Anticancer Therapy (0038)

Treatment Arm	Arm B: CPT-11+ 5-FU/LV N=231 (%)	Arm C: 5-FU/LV N=226 (%)	Arm A: CPT-11 N=226 (%)
Any Prior Therapy	213 (92)	204 (90)	204 (90)
Surgery	182 (79)	182 (81)	180 (80)
Surgery+Chemotherapy	24 (10)	17 (8)	21 (9)

Prior Adjuvant 5-FU
   No
   Yes
	
	206 (89)
	25 (11)
		
		208 (92)
		18 (8)
			
			203 (90)
			23 (10)

There were significantly more patients in Arm B: CPT-11+5-FU/LV who had prior surgery but more patients in Arm A:CPT-11 who had prior radiation therapy.

Efficacy

Time to Tumor Progression (Primary Efficacy Endpoint)

- Plan: Approximately 220 patients in each arm to have 80% power to show a difference of two months in time to progression (5 to 7 months) to be declared significant with a type I error of 0.05 by a 2-sided test.

- Analyzed in the ITT Populations of Arms B and C by non-parametric methods (log-rank test, Kaplan Meier Curves, and by Cox model) in order to take into account relevant covariates.

- Censored: Patients who do not have objective evidence of tumor progression and who are removed from study, who die of causes not related to colorectal cancer, or who are given antitumor treatment other than study treatment.

Table 35. Sponsor Analysis of Time to Tumor Progression (ITT)
Study 0038

Arm	No. of Pts.	No. of Failures	Time to Tumor Progression (months)			p-value
			Median	95% CI	Range	
B	231	174	7	5.4-8.0	0.4-31.4	**0.004**
C	226	171	4.3	3.7-4.6	0.4-20.2	
A	226	165	4.2	3.9-5.0	0.3-18	

(summarized from NDA 20-571, vol 11, p. 81)

- The effect of treatment on TTP in the context of patient baseline characteristics was analyzed using corrected Cox regression modeling. The most predictive factors for improved TTP were normal LDH, fewer involved organ sites, better performance status, normal bilirubin, higher hemoglobin ($11 g/dl) and older age (>65). Treatment with combination of CPT-11 +5-FU/LV in Arm B remained a significant independent predictor of enhanced TTP when significant baseline patient characteristics were taken into account (HR= 0.64, 95% CI 0.51-0.79).

### Survival (Secondary Efficacy Endpoint)

- Logrank test and Kaplan Meier Curves were used to assess survival, stratified logrank test and Cox regression approach to explore the influence of baseline patient characteristics

> ***Reviewer's comment***: *Note that overall survival was added as a secondary endpoint two years after the study started; therefore, the cut-off date for survival analysis was not strictly pre-specified. Enrollment for this study ended in May 1998. The study report specified a cut-off date for the initial analysis of survival to be on September 6, 1999 (i.e. 16 months after the last patient was enrolled) At this time, 67-78% of the patents were already dead.*

Table 36. Sponsor Analysis of Survival (ITT)
Study 0038 (Cut-off Date Sept. 1999)

Arm	No. of Pts.	No. of Failures (%)	Survival (months)			p-value
			Median	95% CI	Range	
B	231	158 (67)	14.5	12.1-17.1	0.4-31.4	**0.097**
C	226	174 (78)	12.6	11.1-15.0	0.4-34.6	
A	226	166 (73)	12	3.9-5.0	0.4-36.1	

(summarized from NDA 20-571, vol 11, p. 100)

------ Arm A   —— Arm B   -·—·- Arm C
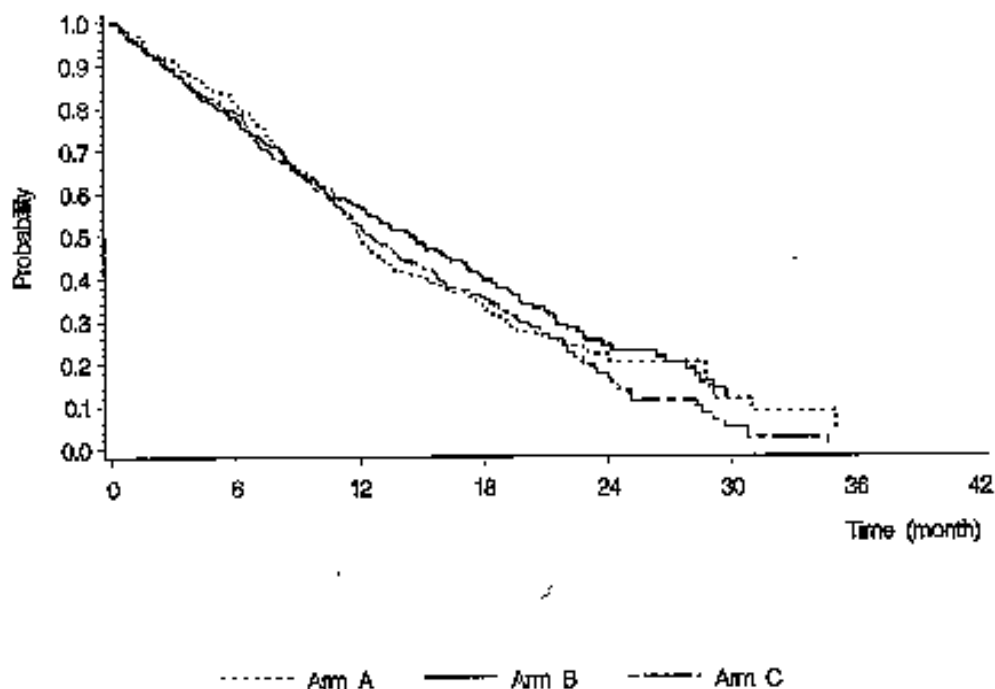
Reviewer's comment: Follow-up survival data was requested by the FDA to verify consistency of the survival differences between treatment arms with more mature data, recognizing the fact that the new cut-off date will be retrospectively identified. The difference in survival between Arm B: CPT-11+5-FU/LV and Arm C: 5-FU/LV approached significance with a p-value of 0.042, hazard ratio of 0.8. This finding is consistent with a positive trend observed with the earlier cut-off date.

Table 37. Sponsor Analysis of Survival (ITT)

Study 0038 (Cut-off Date Dec. 1999)

Arm	No. of Pts.	No. of Failures (%)	Time to Tumor Progression (months)			p-value
			Median	95% CI	Range	
B	231	169 (73)	14.8	5.4-8.0	0.4-41.1+	**0.042**
C	226	185 (82)	12.6	3.7-4.6	0.4-34.6	**HR=0.8**
A	226	176 (78)	12	3.9-5.0	0.4-38.8	(.65-.99)

(summarized from NDA 20-571, vol 11, p. 100)
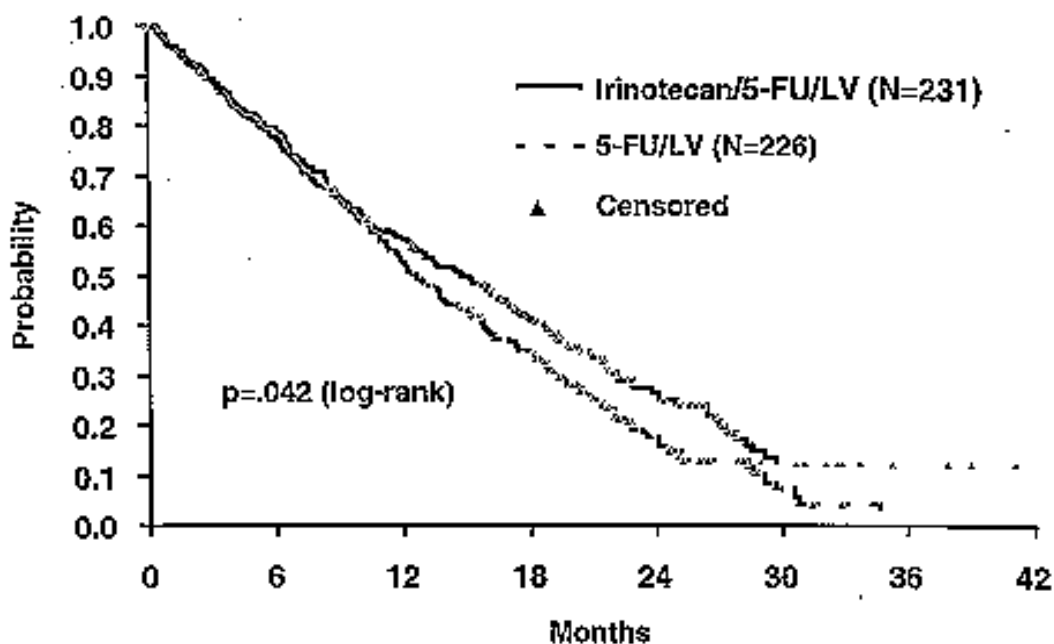
Stratified Analysis of Survival According to Baseline Patient Characteristics (0038)

Prognostic Factor	Arm B: CPT-11+5-FU/LV		Arm C: 5-FU/LV	
	Median	95%CI	Median	95%CI
Age				
<65	14.7	12.4-17.7	11.1	9.2-13.6
$65	14.8	8.6-18.6	15.1	12.6-18.8
Performance Status				
0	21.8	18.4-26.3	16.0	13.6-18.8
>0	9.4	8.2-12.4	10.4	8.2-12.2
Site of Primary Tumor				
Colon	14.7	12.1-17.1	11.9	10.4-13.8
Rectum	16.9	11.5-19.2	15.8	12.3-19.6
No. Of Organ Sites				
1	16.1	13.0-18.6	14.0	12.2-16.2
2	13.6	8.4-21.0	8.0	6.7-11.7
>2	10.6	7.4-16.0	5.1	1.9-18.7
Liver Involvement				
No	15.2	8.4-25.0	17.3	10.8-19.1
Yes	14.5	11.9-17.3	12.0	12.6-24.1
Prior Adjuvant 5-FU				
No	14.8	12.3-17.2	12.1	10.8-14.0
Yes	12.4	5.3-21.6	18.8	12.6-24.1
Serum LDH				
# ULN	26.3	18.9-28.5	16.2	13.0-18.8
>ULN	10.7	9.1-13.6	10.4	7.8-12.3
Hemoglobin				
<11 g/dl	12.0	8.6-14.7	8.6	6.7-11.9
$11 g/dl	17.0	13.6-19.7	13.7	9.0-13.3

Reviewer's comment: Cox regression modeling to evaluate treatment effect on survival in the context of baseline patient characteristics showed that predictive factors for improved survival included fewer involved organs, normal LDH, better performance status, and normal bilirubin. These findings were similar to the findings in Study V303. Treatment with CPT-11 + 5-FU/LV in Arm B was associated with a trend toward lower risk of death when significant baseline patient characteristics were taken into account (HR=0.83, 95% CI 0.67-1.04). In the updated survival data set, the survival difference was statistically significant in the cox model (p = 0.038, HR = 0.80, 0.64-0.99).

Time to Treatment Failure

- The TTF for the ITT population in Arm B: CPT-11+5-FU/LV (median 5.4 months) was significantly improved over that for patients in Arm C: 5-FU/LV (median 3.7 months) (p=0.001 unstratified log-rank test)

Response Rate

- The overall confirmed objective tumor response rate in the ITT population of Arm B: CPT-11+5-FU/LV (39.4%; 9/231) was significantly higher than that in Arm C: 5-FU/LV (20.8%; 47/226). This difference was significant (p<0.0001, chi-square test) with an odds ratio of 2.48 (95% CI, 1.64-3.73).

- As was the case for the time to event variables, the most predictive factors for improved objective tumor response were fewer involved organs, better performance status, and normal bilirubin. Hemoglobin and serum LDH were not significant in this model.

- The median time to response (2.6 vs. 2.8 months) and median duration of response (9.2 vs. 8.7 months) were similar between Arms B and C.

Quality of Life Evaluations

- The EORTC QLQ-C30, a 30-question patient rated linear (1 to 100) scale was used. The 30 items were organized into 5 functional scales (physical, role, emotional, cognitive and social functioning), 3 symptom scales (fatigue, pain, and nausea/vomiting), global health status/QOL scale, and single-item symptom measures (dyspnea, insomnia, loss of appetite, constipation, diarrhea, etc.)

- Protocol Defined Analysis Plan for QOL: Multivariate and univariate repeated measure analyses of variance, scored and validated according to standard procedures recommended by EORTC. Multi-item scales and single item measures were

  - If at least half of the responses to the items of a given scale are available, the missing items will be scored with the mean score of the remaining items for the patient.
  - Descriptive profiles will be generated of the mean QLQ-30 scores over time

  Reviewer's comment: Imputing means for missing observations might introduce bias unless the data are missing at random. There should also be an adequate assessment of dropout patterns by treatment arm.

Patients who responded to the questionnaires at designated weeks of evaluation are summarized in the following table. Observation # 8 coincides with Week 42 on a six-week treatment cycle for Arm B: CPT-11+5-FU/LV, and week 28 on a four-week treatmetn cycle for Arm C: 5-FU/LV. Only a comparison of Arms B and C are presented in the following table:

Table 38. FDA Summary of Compliance with QOL Evaluations by Treatment Arm (Study 0038)

Observation #	Arm B: CPT-11+5-FU/LV		Arm C: 5-FU/LV	
	# Patients Treated (%)[a]	# Responses (%)[b]	# Patients Treated (%)[a]	# Responses (%)[b]
Baseline	225 (100)	223 (99)	217 (100)	217 (100)
2	225 (100)	171 (76)	217 (100)	168 (77)
3	184 (82)	148 (80)	194 (89)	155 (80)
4	156 (69)	127 (81)	154 (71)	134 (87)
5	132 (59)	108 (82)	131 (60)	110 (84)
6	106 (47)	87 (82)	110 (51)	86 (78)
7	92 (41)	67 (73)	86 (40)	73(85)
8	63 (28)	42 (67)	62 (28)	55 (89)

[a] %= # Patients Treated/ Responses
[b] %= # Responses/ # Patients Treated

Regardless of the number of patients being treated, there seems to be a consistent proportion responding to the questionnaires.

- Pain, role functioning, and global health status were selected prospectively by the sponsor to test treatment effect. The analysis of global health status and role functioning indicated that the rate of score change with time was different in the two treatment arms, and a statistically different quantitative interaction was found in the analysis of these two scales. However, the estimated pattern of change was not sufficiently dissimilar so as to result in significant differences between the treatment arms.

    Reviewer's comment: The above scales were added to the protocol as an amendment two years after the protocol opened; therefore, whether these scales were really selected "prospectively" should be qualified.
    The clinical significance of "rate of score change with time" and "pattern of score change" using the 100 point scale in the analyses performed by

> *the sponsor is unclear. The analysis using "change in worst scores" is also unclear.*

- The retrospective analysis using mean values of the worst scores and changes in worst scores from baseline were not impressive with regard to showing an advantage for either treatment arm.

Table 39. Mean Worst Score and Change in Mean Worst Score from Baseline (Study 0038)

Subscale	Arm B: CPT-11+5-FU/LV		Arm C: 5-FU/LV	
	Mean Score	Mean Change	Mean Score	Mean Change
Global Health Status	55	-7	53	-10
Functional Scales				
Physical	66	-10	66	-12
Role	56	-9	55	-14
Emotional	70	-5	68	-5
Cognitive	75	-11	75	-13
Social	62	-8	62	-12
Symptom Scales				
Fatigue	47	10	51	14
Nausea/Vomiting	17	9	19	10
Pain	30	5	37	10
Dyspnea	27	12	27	14
Insomnia	35	5	38	9
Appetite Loss	27	2	37	11
Constipation	23	9	26	9
Diarrhea	28	18	31	21
Financial Problems	26	6	29	8

(NDA 20-571, vol 11, p.109)

> ***Reviewer's comment****: The quality of life assessment tool (QLQ-C30) used in Study 0038 was validated by EORTC[9]. However, specific scales that were considered of interest were identified while the study was ongoing.*

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[9] Aaronaon, et al. The European Organization for Resarch and Treatment fo Cancer QLQ-30: A Quality of Life Instrument for Use in International Clinical Trials in Oncology. JCI, vol.85, No.5, March 1993

Scores obtained from the questionnaires were transformed individually into a value within a 100-point scale and several parameters including change from baseline, change from worst score and variance between observations were described. Since the schedule of QOL testing between treatment arms were different, the mean scores of two observation were imputed in patients treated in Arm C: 5-FU/LV in order to match the timing of QOL testing in patients in Arm B: CPT-11+5-FU/LV. Therefore, although the QOL tool used was previously validated, the methods of data analysis were not pre-specified and clinical significance of the scales used and results are unclear.

It is concerning that the differences in the incidence of severe toxicities (e.g. more severe nausea and vomiting in the CPT-11+5-FU/LV arm or more severe mucositis in the 5-FU/LV arm) were not reflected in the corresponding symptom related quality of life scales. For example, the following question was asked, "Did you vomit in the past week?" The discordance may be due to several reasons including a difference in the time of test administration. While the QOL question asks about the preceding week only, assessment of toxicity at the beginning of treatment includes the whole treatment cycle past. The medications used to alleviate symptoms might be effective enough so as not to show a difference in the symptom directed QOL scales. However, The act of having to take more medications in itself may be viewed as a detriment in quality of life.

Concomitant Medications: *Patients in the CPT-11 treatment groups received more concomitant medications more frequently than patients in Arm C (5-FU/LV). These include the use of antiemetics, anticholinergics, and antidiarrheals. Patients in Arm C (5-FU/LV) received more mouth care products for mucositis. Patients may be receiving more than one type of medication for a particular adverse event and only the common drugs are listed. Note that there is no distinction between prophylactic and therapeutic use of medications.*

Table 40. Concomitant Medications (Study 0038)

	Arm B: CPT-11+ 5-FU/LV N=225 (%)	Arm C: 5-FU/LV N=219 (%)	Arm A: CPT-11 N=223 (%)
Antiemetics			
Dexamethasone	209 (93)	43 (20)	197 (88)
Ondansetron	118 (52)	27 (12)	115 (52)
Prochloperazine	105 (47)	106 (48)	108 (48)
Lorazepam	80 (36)	40 (18)	76 (34)
Ganisetron	77 (34)	19 (9)	75 (34)
Metoclpramide	72 (32)	52 (24)	47 (21)
Diphenhydramine	40 (18)	30 (14)	27 (12)
Others	8 (4)	5 (2)	5 (2)
Anticholinergics			
Atropine	76 (34)	22 (25)	87 (39)
Antidiarrheals			
Loperamide	172 (76)	117 (53)	175 (78)
Diphenoxylate	40 (18)	21 (9)	44 (20)
G-CSF	18 (8)	13 (6)	15 (7)
Stomatologicals	13 (6)	54 (25)	6 (3)

(NDA 20-571, vol. 11, p. 121)

Tertiary Endpoints (Weight and Performance Status)

- Maintenance of weight (no decline of $5% from baseline) and maintenance of performance status (no worsening by $1 point on the ECOG scale) were analyzed in all patients. For each endpoint, the proportions of patients without changes at week 12 in treatment arms B and C were compared by the chi-square test.
- Time to event analysis was also performed. The time from treatment until weight decreased by 5% with respect to baseline and the time until the PS decreased from baseline were analyzed.
-

> *Reviewer's comment*: *The degree of change from baseline weight and performance status were not pre-specified in the original protocol. The clinical significance of a 5% weight change is questionable especially since patients experience severe diarrhea, nausea and vomiting.*

- Performance status was to be assessed within 7 days of the administration of the first dose of study medications, at the beginning of each treatment course, and at the end of treatment. The ECOG scale was used.

- An analysis by the sponsor of change from baseline performance status on Week 12 and time to first decline in performance status did not show differences between treatment arms.

> *Reviewer's comment: Week 12 coincides with the second cycle of treatment and is probably a reasonable point to evaluate changes in patients' performance status.*

Safety (Study 0038)

A descriptive analysis of adverse events was performed on the randomized populations according to the NCI Common Toxicity Criteria. The most frequently reported adverse events in each treatment arm were in the digestive, body as a whole, hemic and lymphatic, and metabolic/nutritional systems.
The following table shows common adverse events (rounded to the nearest whole number).

Table 41. Summary of Toxicity, Study 0038

	ARM B: CPT-11+5-FU/LV (N=225)(N/%)		ARM C: 5-FU/LV (N=219)		ARM A: CPT-11 (N=223)	
	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4
Anemia	218 (97)	19 (8)	216 (99)	12 (6)	216 (97)	10 (4)
Neutropenia	218 (97)	121 (54)	216 (99)	146 (67)	215 (96)	48 (22)
Thrombocytopenia	216 (96)	6 (3)	216 (99)	6 (3)	214 (96)	4 (2)
Diarrhea						
Late	191 (85)	51 (23)	152 (69)	29 (13)	185 (83)	69 (31)
Early	103 (46)	11 (5)	69 (32)	3 (1)	96 (43)	15 (7)
Nausea	178 (79)	35 (15)	148 (68)	18 (8)	182 (82)	36 (16)
Pain	69 (31)	7 (3)	59 (27)	8 (4)	97 (44)	1 (0.4)
Asthenia	158 (70)	44 (20)	141 (64)	26 (12)	154 (69)	31 (14)
Alopecia	97 (43)	--	56 (26)	2 (1)	102 (46)	1 (.4)
Vomiting	136 (60)	22 (10)	101 (46)	9 (4)	140 (63)	27 (12)
Mucositis	73 (32)	5 (2)	167 (76)	37 (17)	66 (30)	5 (2)
Anorexia	77 (34)	13 (6)	92 (42)	8 (4)	98 (44)	16 (7)
Constipation	93 (41)	7 (3)	69 (32)	4 (2)	72 (32)	1 (0.4)
Abdominal Pain	142 (63)	33 (15)	110 (50)	25 (12)	151 (68)	28 (13)
Fever	94 (42)	4 (2)	71 (32)	8 (4)	97 (44)	1 (.4)
Rectal Disorder	31 (14)	3 (1)	20 (9)	1 (.5)	30 (14)	3 (1)

(Final Study Report, v0038, vol.11, p. 115)

> *Reviewer's comment:* *The CPT-11 containing regimens generally have more frequent and severe diarrhea, nausea, and vomiting. Abdominal pain and rectal disorders (e.g. colitis) were also observed more frequently with the CPT-11 regimens. Severe neutropenia was comparable between Arms B: CPT-11+5-FU/LV and Arm C:5-FU/LV. The incidence of mucositis was higher in Arm C: 5-FU/LV.*

Table 42. Reasons for Treatment Discontinuation Study 0038

	Arm B: CPT-11+5-FU/LV N=231(%)	Arm A:CPT-11 N=226(%)	Arm C: 5-FU/LV N=226(%)
Never Treated	4 (2)	8 (4)	4 (2)
Discontinued Treatment	220 (95)	210 (93)	220 (97)
Progressive disease	167 (72)	162 (72)	151 (67)
Nonfatal toxicity	17 (7)	14 (6)	19 (8)
Consent withdrawn, refused treatment	11 (5)	14 (6)	19 (8)
Improvement	11 (5)	3 (1)	7 (3)
Death	10 (4)	10 (4)	8 (4)
Others	4 (2)	5 (2)	4 (2)
Still On Treatment	7 (3)	8 (4)	2 (1)

(Final Study Report, 0038, vol.11 p.68)

Death within 30 Days of Treatment

The frequency of on-study deaths was 9 % (21/225) in Arm B: CPT-11+5-FU/LV, 7% (15/219) in Arm C: 5-FU/LV, and 6% (13/223) in Arm A:CPT-11. The primary reason for on-study deaths is disease progression. Drug related deaths were reported in 2 of the 225 patients (0.9%) in Arm B: CPT-11+5-FU/LV and 3 of the 219 patietns (1.4%) in Arm C: 5-FU/LV.

Hospitalizations

Table 43. Hospitalizations, Study 0038

	Arm B: CPT-11+5-FU/LV N=225	Arm C: 5-FU/LV N=219	Arm A:CPT-11 N=223
At Least 1 Hospitalization	114 (50)	86 (39)	99 (44)
No. of Hospitalizations			
0	112 (50)	133 (61)	124 (56)
1	68 (30)	60 (27)	71 (32)
2	28 (12)	20 (9)	21 (9)
>2	17 (8)	6 (3)	7 (3)
Duration of Hospitalization (days)			
1	6 (3)	2 (2)	2 (1)
2-4	77 (40)	40 (33)	47 (33)
5-7	39 (20)	34 (28)	33 (23)
>7	71 (37)	46 (38)	59 (42)
Unknown	--	--	1 (.7)
Total No. of Hospitalizations	**193**	121	142

> *Reviewer's comment: There were more patients hospitalized and a higher total number of hospitalizations in Arm B: CPT-11+5-FU/LV. However, is seems like the differences were mainly due to hospitalizations of shorter duration (2-4 days).*

Figure 2. FDA Reviewer's Summary of Benefits, Risks and Concerns Study 0038

BENEFITS/ STRENGTHS	RISKS/ WEAKNESSES	CONCERNS/ UNCERTAINTIES
Study Design and Conduct • Large, randomized, well-controlled • Well established control arm • Prognostic factors well-balanced between treatment arms • Well-balanced patient population		• Uncertainty of 5-FU/LV contribution in the experimental arm
Efficacy • Well-controlled and appropriate censoring • Trend toward significant median survival advantage favoring CPT-11 • Statistically significant advantage favoring the CPT-11 combination in TTP, RR (and survival in the update analysis)		
Applicant "Clinical Benefit" analyses	• More frequent use of antidiarrheals, antiemetics and anticholinergics • Retrospective analyses	• No significant difference between treatment arms

BENEFITS/ STRENGTHS	**RISKS/ WEAKNESSES**	**CONCERNS/ UNCERTAINTIES**

"Quality of Life"

• QOL Instrument well validated • Good patient compliance	• Transformation of raw data to a 100-point scale with unclear clinical significance • Retrospective analysis	• Extensive use of concomitant medications possibly responsible for absence of difference in QOL

Safety

• mucositis was higher in Arm C: 5-FU/LV. • Rate of severe neutropenia comparable between Arms B:CPT-11+5-FU/LV and Arm C:5-FU/LV	• more frequent and severe diarrhea, nausea, and vomiting, abdominal pain and rectal disorders (e.g. colitis) • Higher on-study deaths • More patients hospitalized and a higher total number of hospitalizations	

SUMMARY

In two randomized trials the sponsor has demonstrated that CPT-11 adds to the efficacy of regimens of 5FU plus leucovorin in the first-line treatment of metastatic colon cancer. In the initial survival analysis of the US trial, the CPT-11 regimen showed a trend toward increased survival compared to the Mayo 5-FU/LV regimen and in the updated analysis it showed a statistically significant increase in survival. All analyses of response and time to progression showed significant differences in favor of the CPT-11 regimen. In the European trial, both the original and updated survival analyses demonstrated significantly superior survival for the CPT-11 regimens. This difference was even statistically significant in one of the 2 major treatment subgroups: the group receiving the DeGramont regimen. In the subgroup analysis of patients receiving the AIO regimen, there was a similar trend in survival in favor of the CPT-11 arm, but this subgroup analysis did not demonstrate a statistically significant difference. Again, in the European trial, analyses of response and time to progression were significantly in favor of the CPT-11 arm.

As expected, there were frequent and more severe toxicity in the CPT-11/5-FU/LV arms of both studies. There was significantly more severe neutropenia, cholinergic symptoms, diarrhea, nausea, vomiting and asthenia. There were more patients and more frequent hospitalizations in the CPT-11+5/FU/LV arm. On-study deaths were less than 10%, but treatment related deaths were less than 2% in both studies. In study 0038, the incidence of adverse events in the CPT-11+5-FU/LV arm was similar to the CPT-11 alone arm except for hematologic toxicity.

Data from these two clinical trials constitute compelling evidence that CPT-11 in combination with regimens containing 5FU and Leucovorin is efficacious. Side effects were more frequent and more severe. A challenging question is which of these regimens should be recommended in the dosage and administration section. Clearly, the CPT-11-Roswell Park-like regimen (Arm B of Study 0038) should be included since it produced benefit compared to the Mayo Clinic regimen (Arm C of Study 0038), the only 5-FU/LV regimen currently approved. It also seems that the CPT-11-deGramont regimen should be recommended, since it demonstrated a clear survival advantage compared to an active control. However, whether the CPT-11-AIO regimen should be recommended is debatable. The toxicity was greater and the number of patients was inadequate to independently substantiate the CPT-11 contribution to efficacy.

_____   _____
Isagani Mario Chico, MD   date

_____   _____
Grant Williams, MD   date