Pharmacia

ONCOLOGIC DRUGS ADVISORY COMMITTEE BROCHURE

Therapy of Colorectal Cancer with Combination Regimens of CAMPTOSAR® (Irinotecan, CPT-11), 5-Fluorouracil, and Leucovorin

NDA 20-571

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Chemotherapy Regimens Described in this Document

Regimen	Drugs*	Starting Doses	Cycle Schedule
5-FU/LV Bolus Regimens			
Mayo Clinic	LV 5-FU	20 mg/m^2 IV bolus 425 mg/m^2 IV bolus	Daily for 5 days (Days 1-5) in 4-week cycles
Roswell Park	LV 5-FU	500 mg/m^2 IV over 2 hours 500-600 mg/m^2 IV bolus	Weekly for 6 weeks in 8-week cycles
5-FU/LV Infusional Regimens			
AIO	LV 5-FU	500 mg/m^2 IV over 2 hours 2,600 mg/m^2 IV over 24 hours	Weekly for 6 weeks in 7-week cycles
de Gramont	LV 5-FU	200 mg/m^2 IV over 2 hours 400 mg/m^2 IV bolus, then 600 mg/m^2 IV over 22 hours	Day 1, 2 Day 1, 2 Biweekly x 3 in 6-week cycles
Irinotecan/5-FU/LV Bolus Regimens			
Saltz	Irinotecan LV 5-FU	125 mg/m^2 IV over 90 minutes 20 mg/m^2 IV bolus 500 mg/m^2 IV bolus	Weekly for 4 weeks in 6-week cycles
AIO	Irinotecan LV 5-FU	80 mg/m^2 IV over 90 minutes 500 mg/m^2 IV over 2 hours 2,300 mg/m^2 IV over 24 hours	Weekly for 6 weeks in 7-week cycles
Douillard	Irinotecan LV 5-FU	180 mg/m^2 IV over 90 minutes 200 mg/m^2 IV over 2 hours 400 mg/m^2 IV bolus, then 600 mg/m^2 IV over 22 hours	Day 1 Day 1, 2 Biweekly x 3 in 6-week cycles Day 1, 2

* For each regimen, agents are listed in the order in which administered.
Abbreviations: 5-FU = 5-fluorouracil, AIO = Association of Medical Oncology of the German Cancer Society, IV = intravenous, LV = leucovorin

Executive Summary

In April 2000, the FDA approved use of irinotecan (CPT-11, CAMPTOSAR® injection) in combination with 5-fluorouracil (5-FU) and the 5-FU potentiator, leucovorin (LV), as a new reference standard in the first-line therapy of metastatic colorectal cancer. The results from 2 randomized, well-controlled trials formed the basis for approval. One of these studies (Study 0038) was conducted primarily in North America and evaluated the Saltz regimen, a combination of irinotecan with *bolus* 5-FU/LV administration. This regimen was compared to the Mayo Clinic bolus 5-FU/LV regimen that had been a long-standing regulatory and community standard in the US. The other study (Study V303) was conducted primarily in Europe, and evaluated the AIO and Douillard regimens, combinations of irinotecan with *infusional* 5-FU/LV administration. These regimens were compared to infusional 5-FU/LV regimens that had been customarily used in Europe. Each of these studies documented tumor control and survival benefits with irinotecan/5-FU/LV versus the relevant 5-FU/LV control arm.

Since its approval, use of irinotecan/5-FU/LV has gained wide acceptance in the US. This combination is given to the majority of patients undergoing first-line therapy of metastatic colorectal cancer. In US community practice, the Saltz irinotecan/5-FU/LV bolus regimen is used in >95% of patients who receive the 3-drug combination. The Saltz irinotecan/5-FU/LV regimen has also been employed in the conduct of a number of trials with new agents being tested as potential therapies for this disease.

One such study, N9741 (conducted primarily by the North Central Cancer Treatment Group [NCCTG]), has assessed chemotherapies for the first-line treatment of colorectal cancer. It has compared a control arm of the Saltz irinotecan/5-FU/LV regimen with 2 experimental arms employing oxaliplatin/5-FU/LV and irinotecan/oxaliplatin. Another study, C89803 (conducted primarily by the Cancer and Leukemia Group B [CALGB]), has assessed chemotherapies for the adjuvant treatment of patients with Stage III colon cancer. It has compared an experimental arm of the Saltz irinotecan/5-FU/LV regimen with a control arm comprising the Roswell Park weekly bolus regimen of 5-FU/LV. In late April 2001, these 2 ongoing cooperative group trials suggested an apparently higher risk of early death than had been anticipated.

In assessing the number of deaths, the investigators used a new statistic, the mortality rate based on *all deaths of any cause occurring within 60 days from start of therapy*. This statistic had been developed in the framework of the recent implementation of a rapid-reporting system for adverse events. When assessing patients receiving the Saltz irinotecan/5-FU/LV regimen using this method, there were a total of 13 deaths in 289 patients (4.5%) on N9741 and 15 deaths in 635 patients (2.4%) on C89803. Because the method of determining mortality rates was new, placing these results in context with past clinical trial data was difficult. The cooperative group investigators contrasted their findings with the published investigator-designated, treatment-related deaths in the US registration study, ie, 2 deaths in 225 patients (0.9%) receiving the Saltz irinotecan/5-FU/LV regimen and 3 deaths in 219 patients (1.4%) receiving the Mayo Clinic 5-FU/LV regimen. This prompted Pharmacia to calculate the 60-day, all-cause mortality rates in Study 0038. In this study 15 of 225 patients (6.7%) receiving the Saltz regimen and 16 of 218 patients (7.3%) receiving the Mayo Clinic regimen died within the

first 60 days, irrespective of cause. Thus, in the first-line metastatic therapy setting, the 60-day, all-cause mortality rates observed in the N9741 study were actually lower than those observed in any of the arms of Study 0038.

In the adjuvant setting, the 60-day, all-cause mortality findings from the C89803 adjuvant trial were also of concern. Because potential vulnerabilities to toxicity for patients in the post-surgical adjuvant setting are different from the potential risks in the metastatic setting, it was difficult to draw conclusions regarding the implications of the adjuvant findings when applied to the metastatic setting. It was felt that only with mature results would it be possible to determine the full benefit and risk of adjuvant irinotecan/5-FU/LV and that in the interim, irinotecan/5-FU/LV use as adjuvant therapy should remain investigational.

The cooperative groups, the US National Cancer Institute, and Pharmacia worked to convene an independent panel of colorectal cancer experts (chaired by Mace Rothenberg) to review the records of patients who had died on these trials. Based on their deliberations, the panel members suggested the need for closer patient monitoring, improved supportive care measures (particularly antibiotic support), and alterations in dose modification guidelines.

In addition, Pharmacia obtained early mortality data from multiple past and ongoing randomized studies of 5-FU/LV and irinotecan/5-FU/LV in order to place the results from Studies 0038, V303, N9741, and C89803 into perspective. A summary of the results in the first-line therapy of metastatic colorectal cancer are shown in the following table.

Summary of 60-day Mortality by Regimen and Study in First-Line Therapy for Metastatic Colorectal Cancer – Cooperative Group and Industry-Sponsored Studies

Regimen	Drugs	Studies	N	60-Day, All-Cause Mortality, %	
				Rate	95%CI
Historical Experience					
Mayo Clinic	5-FU/LV	7 studies	1593	6.5	4.1- 9.0
Roswell Park	5-FU/LV	6 studies	1085	7.6	4.1-11.1
de Gramont	5-FU/LV	2 studies	253	5.5	2.3- 8.8
Registration Study Experience					
Mayo Clinic	5-FU/LV	Study 0038	219	7.3	4.2-11.6
Saltz	Irinotecan/5-FU/LV	Study 0038	225	6.7	3.8-10.8
de Gramont	5-FU/LV	Study V303	143	1.4	0.2- 5.0
Douillard	Irinotecan/5-FU/LV	Study V303	145	2.1	0.4- 5.9
Post-registration Experience					
Saltz	Irinotecan/5-FU/LV	5 studies*	702	3.8	1.3- 6.2
Douillard	Irinotecan/5-FU/LV	4 studies	191	2.6	0.0- 6.9

Summary estimates (including 95%CIs) are computed using weighted averages of the individual study estimates (see Display 7, page 16) and their standard deviations. Exact 95%CI were computed for the individual studies.

* Includes NCCTG Study N9741

Abbreviations: 5-FU = 5-fluorouracil, CI = confidence interval, LV = leucovorin,

As noted in the table, the historical 60-day, all-cause mortality rate among thousands of patients receiving various 5-FU/LV regimens (eg, Mayo Clinic bolus, Roswell Park bolus, and de Gramont infusional regimen) for metastatic disease has generally been in the range of 5-8%. The early mortality data from both the control arms and the treatment arms of the registration studies (Studies 0038 and V303) are similar to those observed in the historical experience. Since its registration, continued use of either the Saltz or Douillard irinotecan/5-FU/LV regimens in clinical trials has been associated with low mortality rates. Among 702 patients receiving Saltz irinotecan/5-FU/LV for metastatic colorectal cancer in post-marketing trials (including Study N9741), the 60-day, all-cause mortality rate – 3.8% (95%CI:1.3-6.2) – has been comparable to the rate observed with 5-FU/LV alone. The 60-day death rate in 191 patients who have received the Douillard regimen in the post-registration trials– 2.6% (95%CI: 0.0-6.9) – have also been similar to those previously observed.

Pharmacia has also reviewed the safety data from Studies 0038 and V303 to evaluate for risk factors that would indicate a high likelihood of early serious or fatal adverse events. This review indicates that over two-thirds of patients with performance status 2 who received either the Saltz irinotecan/5-FU/LV bolus regimen or the Douillard irinotecan/5-FU/LV infusional regimen experienced first-cycle neutropenic fever or infection, hospitalization, discontinuation due to an adverse event, or death. In addition, such patients were less likely to experience therapeutic benefit.

With the availability of the independent review committee report and these additional analyses, Pharmacia has proposed to make changes to the CAMPTOSAR product labeling. It was agreed by Pharmacia and the FDA that it would be helpful to review the proposed changes with the Oncologic Drugs Advisory Committee (ODAC).

Conclusions

- The 2 adequate and well controlled trials (Studies 0038 and V303) have clearly documented that irinotecan/5-FU/LV provides consistent and measurable benefit to patients with metastatic colorectal cancer by significantly improving tumor shrinkage, prolonging tumor control, and lengthening survival relative to 5-FU/LV alone.
- With appropriate patient selection and supportive care, either the Saltz or Douillard combination regimen can be given safely for metastatic disease, extending life while maintaining quality of life.
- The survival benefits with first-line irinotecan/5-FU/LV over 5-FU/LV alone were observed despite the fact that most patients treated with first-line 5-FU/LV in the control arms of Studies 0038 and V303 received second-line treatment with irinotecan and/or oxaliplatin.
- The data from multiple prior studies indicate that the 60-day, all-cause mortality rates from Studies 0038, V303, and N9741 are no different from those associated with the use of 5-FU/LV in the first-line treatment of metastatic colorectal cancer.
- Available data from post-marketing trials (including Study N9741) employing the Saltz and Douillard irinotecan/5-FU/LV regimens document early mortality rates that continue to be as low as any attained in prior studies with 5-FU/LV when used as therapy of metastatic colon cancer.

- Collectively, these results indicate that reverting to first-line therapy with 5-FU/LV alone will not protect patients who are at risk from early treatment- or disease-related mortality, and it will deny improved tumor control and survival benefits to many patients.
- No definitive randomized comparisons of the Saltz and Douillard irinotecan/5-FU/LV regimens have been performed. Therefore, it is difficult to draw firm conclusions about the relative merits of these 2 methods of treatment administration.
- The availability of both the Saltz irinotecan/5-FU/LV bolus regimen and the Douillard irinotecan/5-FU/LV infusional regimen offers patients and physicians flexibility in the method of administration. Retention of both of these regimens in product labeling permits Pharmacia to continue educating physicians in the safest use of these regimens in clinical practice. Retention of both of these regimens as regulatory standards will allow the greatest flexibility in the design of trials testing new therapies for this life-threatening disease.
- Additional information obtained from registration trials and post-marketing studies regarding patient selection, patient monitoring, supportive care, and dose modifications should be included in the CAMPTOSAR package insert.

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1. REGISTRATION STUDIES

1.1 Second-line Therapy of Metastatic Colorectal Cancer

Irinotecan hydrochloride injection (CPT-11, CAMPTOSAR® injection) is an antineoplastic agent topoisomerase I inhibitor with broad activity in colorectal cancer and other tumors [Pommier 1994]. Irinotecan was originally developed in Japan by the Yakult Honsha Company. Licensing rights for clinical development in the United States (US) were granted to Pharmacia, whereas similar rights in Europe were granted to Aventis.

Irinotecan was first approved in the US for the treatment of metastatic colorectal cancer after failure of first-line treatment with 5-fluorouracil (5-FU), a cytotoxic thymidylate synthase inhibitor that – until the advent of irinotecan – had been the only available treatment [Grem 2001]. This initial approval was based on tumor response rate data from phase II, uncontrolled studies [Dietz 1995a-c, Shimada 1993, Mahjaoubi 1994, Blanc 1996]. Conditional marketing authorization in the US was granted in 1996 under Food and Drug Administration (FDA) regulations designed to accelerate approval of new and promising drugs for serious or life-threatening illnesses.

Subsequently, Aventis completed 2 European randomized, phase III studies comparing second-line irinotecan therapy with best supportive care [Jacques 1997a] or with infusional 5-FU-based therapy [Jacques 1997b] and provided the data from these trials to Pharmacia. The survival advantages associated with irinotecan use in each of these trials were the basis for full FDA approval for irinotecan as second-line therapy for patients with metastatic colorectal cancer in September 1998.

1.2 First-line Therapy of Metastatic Colorectal Cancer

In the first-line therapy of colorectal cancer, 2 phase III, randomized, controlled, multicenter, multinational, clinical trials were conducted to evaluate whether the combination of irinotecan with 5-FU/LV would improve tumor control and survival relative to standard 5-FU/LV alone in patients with previously untreated metastatic colorectal cancer. The results of these trials were the basis for approval of irinotecan in combination with 5-FU/LV as first-line therapy of metastatic colorectal cancer in April 2000.

1.2.1 Study Methods

One of the registration studies (Study 0038) [Miller 1999]) was sponsored by Pharmacia and evaluated use of irinotecan in combination with bolus 5-FU/LV. In this study, patients were stratified by age (<65 years versus ≥65 years), performance status (0 versus 1-2), prior adjuvant 5-FU-based therapy (yes versus no), and the time from the initial diagnosis (<6 months versus ≥6 months). Patients were randomly allocated to receive one of 3 regimens (Display 1).

Display 1. Treatment Regimens – Study 0038

Arm (Regimen)	Drugs*	Starting Doses	Cycle Schedule
A†	Irinotecan	125 mg/m^2 IV over 90 minutes	Weekly for 4 weeks in 6-week cycles
B (Saltz)‡	Irinotecan LV 5-FU	125 mg/m^2 IV over 90 minutes 20 mg/m^2 IV bolus 500 mg/m^2 IV bolus	Weekly for 4 weeks in 6-week cycles
C (Mayo Clinic)§	LV 5-FU	20 mg/m^2 IV bolus 425 mg/m^2 IV bolus	Daily for 5 days (Days 1-5) in 4-week cycles

* For each regimen, agents are listed in the order in which administered.
† [Dietz 1995d-e], ‡ [Saltz 1996], § [Poon 1989]
Abbreviations: 5-FU = 5-fluorouracil, IV = intravenous, LV = leucovorin

The second study (Study V303) [Gruia 1999] was sponsored by Aventis and evaluated 2 different methods of administering infusional 5-FU/LV, with or without irinotecan (Display 2). In this trial, patients were randomized within study center.

Display 2. Treatment Regimens – Study V303

Arm (Regimen)		Drugs*	Starting Doses	Cycle Schedule
A	A1 (AIO)†	Irinotecan LV 5-FU	80 mg/m^2 IV over 90 minutes 500 mg/m^2 IV over 2 hours 2,300 mg/m^2 IV over 24 hours	Weekly for 6 weeks in 7-week cycles
	A2 (Douillard)‡	Irinotecan LV 5-FU	180 mg/m^2 IV over 90 minutes 200 mg/m^2 IV over 2 hours 400 mg/m^2 IV bolus, then 600 mg/m^2 IV over 22 hours	Day 1 Day 1, 2 Biweekly x 3 in 6-week cycles Day 1, 2
B	B1 (AIO)§	LV 5-FU	500 mg/m^2 IV over 2 hours 2,600 mg/m^2 IV over 24 hours	Weekly for 6 weeks in 7-week cycles
	B2 (de Gramont)¶	LV 5-FU	200 mg/m^2 IV over 2 hours 400 mg/m^2 IV bolus, then 600 mg/m^2 IV over 22 hours	Day 1, 2 Day 1, 2 Biweekly x 3 in 6-week cycles

*For each regimen, agents are listed in the order in which administered.
† [Vanhoefer 1999], ‡ [Mery-Mignard 1999], § [Weh 1988, Köhne 1998], ¶ [de Gramont 1997]
Abbreviations: 5-FU = 5-fluorouracil, AIO = Association of Medical Oncology of the German Cancer Society, IV = intravenous, LV = leucovorin

In Study V303, individual study sites were to determine in advance whether they preferred to use the AIO (A1/B1) regimens or the Douillard/de Gramont (A2/B2) regimens. Once decided, patients at the A1/B1 sites were only to be randomized to Regimens A1 versus B1, and patients at the A2/B2 sites were only to be randomized to Regimens A2 versus B2.

In both trials, patients were to receive repeated cycles of treatment until tumor progression or unacceptable toxicity. Tailoring of doses to individual patient tolerance was achieved using defined dose modification criteria. Dose modification rules were different in the 2 trials, in part influenced by the differences in the administration schedules. In Study 0038, treatment during a cycle was reduced by 20% for grade 2 toxicity and omitted for grade 3 or 4 toxicity. Treatment could be resumed once toxicity was resolved to ≤grade 2 but with a reduction by 20% for grade 3 toxicities or by 40% for grade 4 toxicities or neutropenic fever. In Study V303, for patients experiencing grade 4 myelosuppression, neutropenic fever, or grade 3 or 4 nonhematologic toxicity, treatment

was delayed and then reduced by 20% upon resumption of therapy. Further data regarding dose modification criteria are provided in Appendix A, Table 1.

Supportive care in the studies was to include atropine for cholinergic symptoms, loperamide for diarrhea, and antiemetics for nausea and/or vomiting. Use of colony-stimulating factors was permitted but not advocated. In Study V303, it was specified that oral antibiotic therapy with a fluoroquinolone was to be given to patients who developed grade 4 neutropenia and to those who developed grade 3-4 neutropenia or fever in association with diarrhea. Such therapy was not formally recommended in Study 0038 but was permitted.

Patients enrolled to the studies included those with a histologic diagnosis of metastatic colorectal cancer; measurable tumor lesions; no prior treatment for metastatic disease, a performance status of 0, 1, or 2; and adequate organ function. Study V303 differed from Study 0038 in having an upper age limit restriction (age ≤75), more stringent criteria for bone marrow function, a lesser requirement regarding time from prior adjuvant chemotherapy (>6 months for Study V303 and >12 months for Study 0038), and no proscription against prior radiotherapy to the abdomen or pelvis. Further data regarding enrollment criteria are provided in Appendix A, Table 2.

Both studies employed standard analytical techniques to evaluate confirmed objective tumor response rates, time to tumor progression (TTP), time to treatment failure (TTF), survival, safety, and quality of life as assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

1.2.2 Study Results

1.2.2.1 Patients

Study 0038 enrolled and randomized a total of 683 patients between May of 1996 and May of 1998 at 71 sites (primarily in the US and Canada). Study V303 enrolled and randomized a total of 387 patients between May of 1997 and February 1998 at 83 sites (primarily in Europe). In Study V303, the distribution of patients by regimen was AIO (A1/B1, n = 53/44) and Douillard/deGramont (A2/B2, n = 145/143). Minimum follow-up was ≥19 months in both trials. Further data regarding patient disposition by study, treatment arm, and regimen are provided in Appendix A, Table 3.

Baseline patient characteristics for the intent-to-treat populations assessed for efficacy are provided in Display 3. For the sake of ease in review, the data from the 2 trials are presented side by side. Further data regarding the baseline patient characteristics by study, treatment arm, and regimen for the intent-to-treat patient populations and the as-treated patient populations are provided in Appendix A, Table 4 and Table 5, respectively.

Display 3. Patient Characteristics by Study and Treatment Arm – Studies 0038 and V303 (Intent-to-Treat Populations)

Patient Characteristic*	Study 0038		Study V303	
	Saltz Irinotecan Bolus 5-FU/LV	Mayo Clinic Bolus 5-FU/LV	AIO/Douillard Irinotecan Infusional 5-FU/LV	AIO/de Gramont Infusional 5-FU/LV
	Arm B N = 231	Arm C N = 226	Arm A N = 198	Arm B N = 187
Median Age in years (range)	62 (25-85)	61 (19-85)	62 (27-75)	59 (24-75)
Gender (%)				
Male	65.4	54.4	66.7	52.9
Female	34.2	44.7	33.3	47.1
Performance Status (%)				
0	38.5	41.2	51.5	51.3
1	45.9	45.1	41.9	41.2
2	15.2	12.8	6.6	7.5
Prior Adjuvant Therapy (%)	10.8	8.0	25.8	23.5
Radiotherapy Therapy (%)	3.0	2.2	20.2	15.5
Laboratory Abnormalities (%)†				
LDH >ULN	60.0	55.7	43.0	44.9
SGOT >ULN	28.7	25.4	22.0	21.1
Total Bilirubin >ULN	6.6	4.1	6.6	7.0
WBC ≥8 x 10^3/mm^3	52.4	53.0	47.2	38.0
Hemoglobin <11 g/dL	25.6	25.3	16.2	21.4
Creatinine >ULN	7.1	3.7	5.1	6.0

* Data not available for some patients who were randomized but not treated.
† Percentage of patients with data available
Abbreviations: 5-FU = 5-fluorouracil, LDH = lactate dehydrogenase, LV = leucovorin, SGOT = serum glutamate-oxalate transferase, ULN = upper limit of normal, WBC = white blood count

Within studies, patient characteristics for important prognostic factors were balanced. However, there was more functional impairment and organ dysfunction among patients enrolled in the irinotecan/5-FU/LV and 5-FU/LV arms of Study 0038 than among patients enrolled to Study V303. Relative to Study V303, Study 0038 patients were older (there were 44 patients >75 years of age enrolled in Study 0038 versus none in Study V303); a lower proportion of patients had performance 0; a higher proportion of patients had performance status 2; and a greater proportion of patients had adverse laboratory prognostic factors (eg, elevated serum LDH, abnormal SGOT, increased WBC, or low hemoglobin).

1.2.2.2 Tumor Control and Survival

Efficacy data from the intent-to-treat populations of the registration studies are presented in Display 4. Further efficacy information by study, treatment arm, and regimen is provided in Appendix A, Table 6.

Display 4. Efficacy by Study and Treatment Arm – Studies 0038 and V303 (Intent-to-Treat Populations)

Endpoint	Study 0038		Study V303	
	Saltz Irinotecan Bolus 5-FU/LV	Mayo Clinic Bolus 5-FU/LV	AIO/Douillard Irinotecan Infusional 5-FU/LV	AIO/de Gramont Infusional 5-FU/LV
	Arm B N = 231	Arm C N = 226	Arm A N = 198	Arm B N = 187
Confirmed* Objective Tumor Response Rates, %	39.4	20.8	34.8	21.9
	(p<0.001)†		(p<0.005)†	
Median Duration of Objective Tumor Response, months	9.2	8.7	9.3	8.8
	(p=0.369)‡		(p=0.085)‡	
Median TTP, months	7.0	4.3	6.7	4.4
	(p=0.004)‡		(p<0.001)‡	
Median TTF, months	5.4	3.7	5.3	3.8
	(p=0.001)‡		(p=0.001)‡	
Median Survival, months	14.8	12.6	17.4	14.1
	(p=0.042)‡		(p=0.032)‡	

* Confirmed ≥4-6 weeks after first evidence of objective response
† Chi-square test
‡ Unstratified log-rank test
Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin, TTF = time to treatment failure, TTP = time to tumor progression

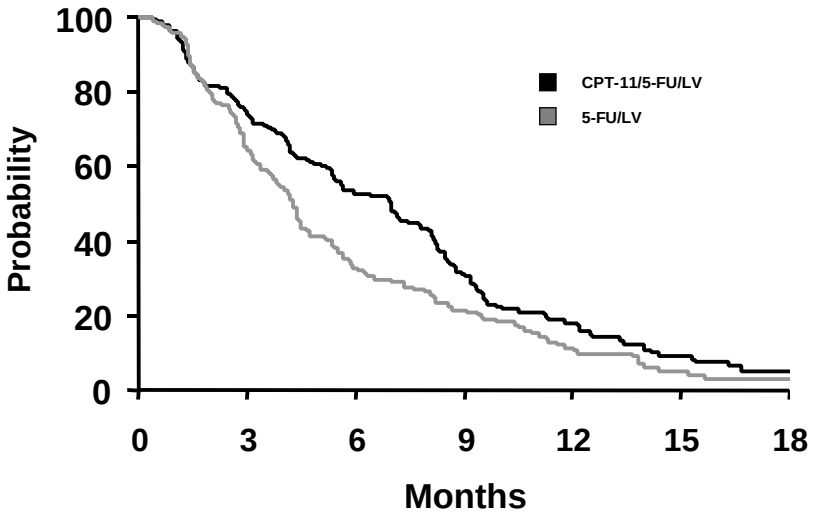
Each trial demonstrated that the combination of irinotecan with 5-FU/LV therapy resulted in significant improvements in tumor control and survival compared with 5-FU/LV alone. The survival benefits associated with irinotecan/5-FU/LV therapy were achieved even though the majority of control patients treated with first-line 5-FU/LV on the studies received active second-line therapy (primarily with either irinotecan- or oxaliplatin-containing treatments). Further information regarding post-study treatment by study and treatment arm is provided in Appendix A, Table 7.

Cox regression modeling indicated that better baseline performance status and normal serum LDH appeared to be the most significant and consistent predictors of improved TTP ($p<0.001$ for both covariates) and survival ($p<0.0001$ for both covariates). The treatment (irinotecan/5-FU/LV versus 5-FU/LV) effect remained significant when accounting for these and other relevant baseline variables (Study 0038, $p=0.038$; Study V303 $p=0.037$) [Miller 1999, Knight 2000].

Figure 1 and Figure 2 show the Kaplan-Meier TTP and survival curves for Studies 0038 and V303, respectively.

Figure 1. TTP – Kaplan-Meier Estimates – Studies 0038 and V303

Study 0038



Study V303

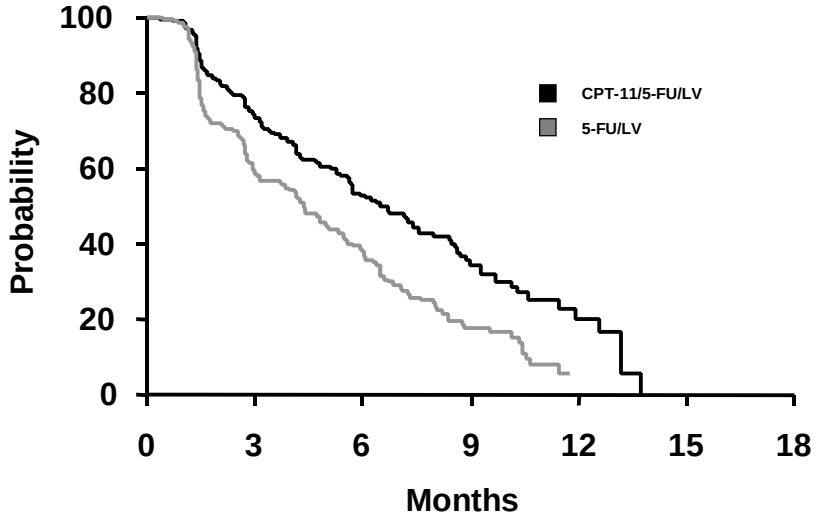
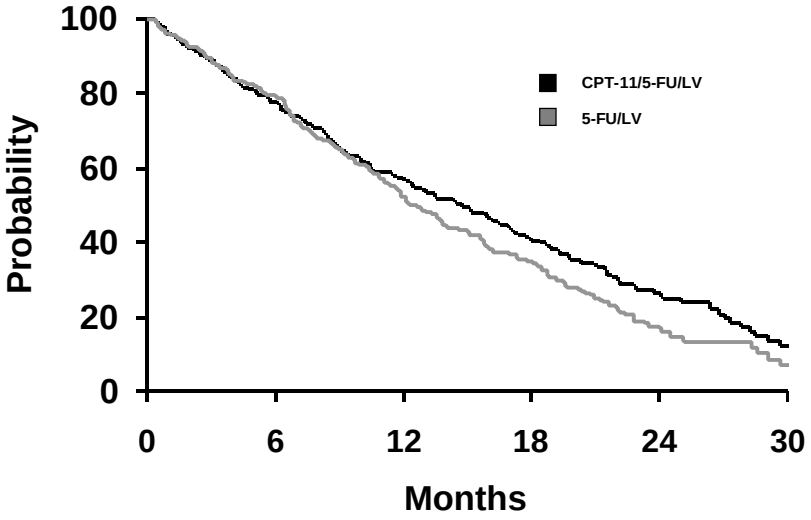
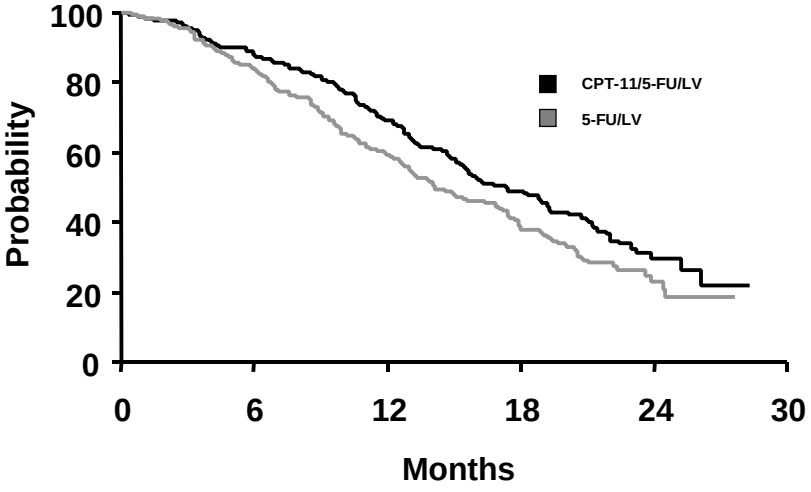


Figure 2. Survival – Kaplan-Meier Estimates – Studies 0038 and V303

Study 0038



Study V303



It is apparent that the irinotecan/5-FU/LV survival curve separates from the 5-FU/LV curve later in Study 0038 than in Study V303. This finding may be explained by the greater proportion of patients with performance status 2 in Study 0038; such patients generally had survival times <6 months with either irinotecan/5-FU/LV or 5-FU/LV therapy. If only patients with baseline performance status 0-1 are considered, survival results for the irinotecan/5-FU/LV arms are quite similar. In Study 0038, median survivals for the irinotecan/5-FU/LV arm (n=195) and the 5-FU/LV arm (n=195) are 17.2 months and 13.8 months, respectively. In Study V303, median survivals for the irinotecan/5-FU/LV arm (n=185) and the 5-FU/LV arm (n=173) are 17.4 months and 15.5 months, respectively.

1.2.2.3 Quality of Life

In both studies, the primary repeated-measures analyses of variance of changes from baseline in EORTC QLQ C-30 quality of life scores showed no significant differences between the irinotecan/5-FU/LV and 5-FU/LV arms. Additional analyses from Study 0038 demonstrated that patients receiving Saltz irinotecan/5-FU/LV fared better than those receiving Mayo Clinic 5-FU/LV for several disease-related subscales, including role functioning, fatigue, appetite loss, and pain, when worst changes from baseline were considered.

1.2.2.4 Safety

Display 5 provides data regarding adverse events in the treated populations from the 2 registration studies. The safety data for the Saltz irinotecan/5-FU/LV and Mayo Clinic 5-FU/LV arms of Study 0038 are shown. Similarly, safety data from the Douillard irinotecan/5-FU/LV regimen and the corresponding de Gramont 5-FU/LV control arms of Study V303 are shown. Death rates (all causes ≤30 days from last treatment and drug-related based on investigator assessment) are those already reported in the current CAMPTOSAR package insert. Further data regarding overall safety; thromboembolic events; deaths and supportive care medication by study, treatment arm, and regimen are provided in Appendix A, Table 8, Table 9, and Table 10, Table 11, respectively.

Display 5. Safety by Study and Treatment Regimen – Studies 0038 and V303 (Treated Populations)

Adverse Event	Study 0038		Study V303	
	Saltz Irinotecan Bolus 5-FU/LV	Mayo Clinic Bolus 5-FU/LV	Douillard Irinotecan Infusional 5-FU/LV	de Gramont Infusional 5-FU/LV
	Arm B N = 225	Arm C N = 219	Arm A2 N = 145	Arm B2 N = 143
Grade 3/4 Diarrhea, %	22.7	13.2	14.4	6.3
Grade 3	*15.1*	*5.9*	*10.3*	*4.2*
Grade 4	*7.6*	*7.3*	*4.1*	*2.1*
Grade 3/4 Vomiting, %	9.7	4.1	3.5	2.8
Grade 3	*5.3*	*2.7*	*2.8*	*1.4*
Grade 4	*4.4*	*1.4*	*0.7*	*1.4*
Grade 3/4 Mucositis, %	2.2	16.9	4.1	2.8
Grade 3	*1.8*	*14.6*	*4.1*	*2.8*
Grade 4	*0.4*	*2.3*	*0.0*	*0.0*
Grade 3/4 Neutropenia, %	53.8	66.7	46.2	13.4
Grade 3	*29.8*	*24.2*	*36.4*	*12.7*
Grade 4	*24.0*	*42.5*	*9.8*	*0.7*
Neutropenic Fever/Infection*, %	16.0	17.4	5.5	0.7
Thromboembolism†, %	9.3	11.4	11.7	5.6
Hospitalizations‡, %	50.2	39.3	40.7	24.5
Discontinuations§, %	7.6	6.4	6.2	0.7
Deaths ≤30 Days from Last Therapy, %	9.3	6.8	4.2	2.8
Cytotoxic or Vascular Events Present	*3.1*	*5.0*	*2.8*	*2.1*
Cytotoxic Events Present ¶	3.1	2.3	1.4	0.0
Vascular Events Present¶	0.4	2.7	2.1	2.1
Progressive Disease or Other Event Present¶	*6.2*	*1.8*	*1.4*	*0.7*
Drug-related Deaths£, %	0.9	1.4	0.7	0.0

* Includes all events of neutropenic fever (concomitant grade 3-4 neutropenia and grade ≥2 fever) and neutropenic infection (concomitant grade 3-4 neutropenia and grade 3-4 infection or sepsis).
† Includes venous and/or arterial events and all instances of sudden death
‡ Includes hospitalization for any cause (whether or not specifically related to toxic effects of study therapy).
§ Includes discontinuations due to adverse events of any type and any potential cause (whether disease- or drug-related).
¶ Monitor assessment
£ Investigator assessment
Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin

In each study, the combination of irinotecan with 5-FU/LV increased the incidence of grade 3-4 diarrhea relative to 5-FU/LV alone. Differences were primarily in the incidence of grade 3 diarrhea; grade 4 diarrhea – often defined by the need for hospitalization for supportive care – was comparably infrequent in the treatment and control arms of Study 0038 (eg, 7.6% with Saltz irinotecan/5-FU/LV and 7.3% with Mayo Clinic 5-FU/LV). The incidence with Douillard irinotecan/5-FU/LV was 4.1%.

As expected, grade 3-4 vomiting was somewhat more common with irinotecan-based therapy than with 5-FU/LV alone, but occurred in <10% of patients in any of the combination arms. The frequency of grade 3-4 vomiting with the Saltz irinotecan/5-FU/LV regimen (9.7%) relative to the Douillard irinotecan/5-FU/LV

regimen (3.5%) may have been the result, in part, of the greater proportion of patients with performance status 2 in Study 0038; the likelihood of severe vomiting was correlated with poor performance status (as documented in Display 9 [page 22]). In addition, it appears that patients in Study 0038 were less likely to get serotonin antagonists as antiemetics than patients in Study V303 (see Appendix A, Table 11).

Grade 3-4 mucositis was quite infrequent with irinotecan-based therapy, occurring in <4% of patients receiving combination treatments. By contrast, the Mayo Clinic 5-FU/LV regimen was associated with a much higher frequency of severe, grade 3-4 mucositis (16.9%).

The Mayo Clinic 5-FU/LV regimen was also associated with the highest rate of grade 3-4 neutropenia (66.7%) and neutropenic fever/infection (17.4%). Treatment with the Saltz irinotecan/5-FU/LV did not increase the risk of either grade 3-4 neutropenia (53.8%) or neutropenic fever/infection (16.0%). In the patients given the Douillard irinotecan/5-FU/LV regimen on Study V303, grade 3-4 neutropenia was relatively common (46.2%) but there was a low likelihood of neutropenic fever/infection (5.5%). As indicated in Display 9 (page 22), the likelihood of neutropenic fever or infection increased with worsened baseline performance status in both studies; given the larger percentage of patients with performance status 2 in Study 0038, this relationship became statistically significant in that study.

The pattern of vascular events across the arms of the 2 studies was not consistent. In Study 0038, patients receiving Saltz irinotecan/5-FU/LV were less likely to have a vascular event (9.3%) than were patients receiving Mayo Clinic 5-FU/LV (11.4%). In Study V303, the irinotecan-containing arms had a higher incidence of vascular events (eg, 11.7% with Douillard irinotecan/5-FU/LV versus 5.6% with de Gramont 5-FU/LV).

Hospitalization sometime during study was a relatively common event in this patient population with advanced cancer undergoing cytotoxic therapy. Within both studies, there was an approximate 10-15% absolute increase in the proportion of patients hospitalized when contrasting irinotecan/5-FU/LV regimens to 5-FU/LV regimens. Cross-study comparisons are difficult given that the baseline performance status and organ function in the 2 studies were different. As indicated in Display 9 (page 22), the likelihood of hospitalization was significantly associated with worsened baseline performance status in both studies.

Discontinuations due to adverse events were similar for irinotecan/5-FU/LV-containing regimens.

Within each study, death rates were well balanced between arms treatment and control arms, no matter how characterized. As with other safety endpoints, cross-study comparisons are difficult given the differences in baseline characteristics between the trials. As documented in Display 9 (page 22), mortality increased with worsened performance status in both studies; this result reached statistical significance in Study 0038.

1.2.3 Conclusions

Attempts at improving outcome in patients with metastatic colorectal cancer with the limited tools of 5-FU and LV had been the source of decades of disappointment [Grem

2001]. These adequate and well-controlled studies or irinotecan/5-FU/LV were the first trials to document that the combination of a new agent with 5-FU/LV could safely benefit patients with metastatic colorectal cancer. By inducing tumor shrinkage and extending tumor control, combined use of irinotecan/5-FU/LV was associated with significantly prolonged life without an impairment of quality of life. When tested against relevant regulatory reference regimens, the results of these trials established irinotecan/5-FU/LV as a new survival standard and offered patients and physicians flexibility in options for delivery of irinotecan/5-FU/LV therapy.

2. POST-MARKETING HISTORY

2.1 General Post-marketing Experience

Since its registration in the US, it has been estimated that approximately 60% of patients undergoing first-line therapy for metastatic colorectal cancer receive the irinotecan/5-FU/LV combination. An estimated 24,000 patients have been treated with irinotecan/5-FU/LV [Tandem 2001]. Consistent with a long-standing US preference for use of bolus regimens in the treatment of colorectal cancer, >95% of patients given combination treatment have received the Saltz irinotecan/5-FU/LV bolus regimen [Tandem 2001]. While there are substantial limitations to post-marketing surveillance data, spontaneous reports of irinotecan/5-FU/LV-related death have been infrequent, with only 2 such observations received from US physicians in the first year following FDA approval.

2.2 Cooperative Group Trials in Colorectal Cancer

In October 1998, the North Central Cancer Treatment Group (NCCTG) opened N9741, a Phase III intergroup trial to compare several investigational combination chemotherapy regimens against 5-FU/LV in patients with metastatic colorectal cancer [N9741 2001, Morton 2001]. The study was amended several times, but since March 2000, it has been a 3-arm study with Saltz irinotecan/5-FU/LV becoming the new control arm. By April 2001, 841 of a planned 1125 patients had been enrolled to the 3 arms of Study N9741: 289 had received Saltz irinotecan/5-FU/LV, 277 had received a combination of oxaliplatin/infusional 5-FU/LV (FOLFOX4) [André 1999] and 275 had received a regimen of irinotecan/oxaliplatin [Wasserman 1999].

In April 1999, the Cancer and Leukemia Group B (CALGB) opened C89803, a Phase III intergroup trial comparing Saltz irinotecan/5-FU/LV versus the Roswell Park weekly bolus regimen of 5-FU/LV [Petrelli 1989] as adjuvant therapy for patients with Dukes' Stage C (TNM Stage III) colon cancer [C89803 2001]. By April 2001, enrollment of 1263 patients had been achieved, meeting the accrual goal of this study: 635 had received Saltz irinotecan/5-FU/LV and 628 had received Roswell Park 5-FU/LV alone.

On April 24, 2001, the NCCTG Monitoring Committee identified what was considered an unexpectedly high number of early deaths among patients enrolled to Study N9741. Using a recently implemented rapid reporting system [Sargent 2000], they assessed the number of deaths occurring from any cause within 60 days from the start of therapy as a means to quantify the mortality rates. Using this mortality statistic, there were a total of 13 deaths in 289 patients (4.5%) treated with Saltz irinotecan/5-FU/LV, 5 deaths in 277

patients (1.8%) treated with oxaliplatin/5-FU/LV, and 5 deaths in 275 patients (1.8%) treated with irinotecan/oxaliplatin [Morton 2001, Rothenberg 2001].

The concern noted by the NCCTG prompted a CALGB internal review of the early death rate on Study C89803. This review identified that 15 of 635 patients (2.4%) treated with Saltz irinotecan/5-FU/LV and 5 of 628 patients (0.8%) treated with Roswell Park 5-FU/LV had died within 60-days of starting adjuvant therapy [Rothenberg 2001]. An additional patient with coronary artery disease who had received irinotecan/5-FU/LV died on Day 82 from a myocardial infarction.

Because the NCCTG method of determining mortality rates was new, comparison with other trials was difficult. At the time of the NCCTG mortality review, no data regarding 60-day, all-cause mortality rates had been reported in prior chemotherapy studies in colorectal cancer. Contrasting the standard Saltz irinotecan/5-FU/LV arms to the experimental oxaliplatin/5-FU/LV or irinotecan/oxaliplatin arms within Study N9741 was not informative since the overall therapeutic benefit of the experimental arms has not been established. As a result, the NCCTG investigators contrasted their 60-day, all-cause mortality figures with the published, investigator-designated treatment-related deaths in the US registration trial (Study 0038), ie, 2 deaths in 225 patients (0.9%) receiving the Saltz irinotecan/5-FU/LV regimen and 3 deaths in 219 patients (1.4%) receiving the Mayo Clinic 5-FU/LV regimen (see Display 5 [page 9]).

This comparison proved to be problematic, as became evident when the 60-day, all-cause mortality rates were computed for the US registration trial (Study 0038). These rates were documented to be 6.7% for the Saltz irinotecan/5-FU/LV regimen, 7.3% for the Mayo Clinic 5-FU/LV regimen, and 6.7% for irinotecan alone. Thus, the 60-day, all-cause mortality rates that caused the initial concern in Study N9741 were actually lower than those observed in any of the arms of Study 0038.

The NCCTG decided to suspend accrual to Study N9741 on April 25, 2001. A decision was made to lower the starting doses of irinotecan and 5-FU in the Saltz irinotecan/5-FU/LV control arm of the study and the trial has since reopened. The accrual goals of Study C89803 had been met and so the trial was closed to new patient entry on April 27, 2001. Patients already enrolled to the C89803 trial remained on therapy with slight adjustments in dose modification guidelines and there have been no further on-treatment deaths [Rothenberg 2001].

2.3 Independent Review Committee

2.3.1 Background and Methods

Representatives of the NCCTG, CALGB, the Cancer Therapy Evaluation Program of the NCI, and Pharmacia agreed that an independent review committee should be convened to review the medical records of the patients who experienced early death on both of the 2 cooperative group studies. Theradex, a contract research firm, was engaged to select panelists and coordinate this review. Pharmacia agreed to provide an unrestricted grant for this purpose.

The review panel had the following membership:

- Mace Rothenberg (Chairman)(Vanderbilt-Ingram Cancer Center, Nashville, TN)
- Neal Meropol (Fox Chase Cancer Center, Philadelphia, PA)
- Elizabeth Poplin (Cancer Institute of New Jersey, New Brunswick, NJ)
- Eric Van Cutsem (University Hospital Gasthuisberg, Leuven, Belgium)
- Scott Wadler (Albert Einstein College of Medicine, Bronx, NY).

Theradex obtained review copies of the complete inpatient and outpatient medical records of each patient. For Study N9741, all records from the time of study registration to the time of death were available. For Study C89803, all records from the time of original surgery to the time of death were available. When accessible, autopsy reports were also included. Each patient record was independently reviewed in detail by a primary reviewer and at least one secondary reviewer. Each case was then discussed by the group to reach a consensus on the cause of death. Deaths were categorized using the following definitions:

- Treatment-induced: Death was clearly caused by protocol treatment.
- Treatment-exacerbated: Death was caused by exacerbation of an underlying medical disorder by protocol treatment. The medical disorder had to be pre-existing at the time of initiation of treatment. The patient's death would not have been expected from the underlying condition had protocol treatment not been administered.
- Treatment-unrelated: Death was clearly unrelated to protocol treatment.

2.3.2 Results

The independent review committee released a detailed report that has been summarized for publication [Rothenberg 2001][please see Appendix B]. Display 6 provides an overview of the committee's categorization of the deaths and assignments of attribution.

Display 6. Mortality by Treatment Arm – Studies N9741 and C89803

Categorization	Study N9741			Study C89803	
	Saltz Irinotecan Bolus 5-FU/LV	Oxaliplatin Infusional 5-FU/LV	Irinotecan Oxaliplatin	Saltz Irinotecan Bolus 5-FU/LV	Roswell Park Bolus 5-FU/LV
	N = 289	N = 277	N = 275	N = 635	N = 628
Deaths ≤60 Days from First Therapy, %	4.5 *	1.8	1.8	2.5 †	0.8
Treatment-Related or -Exacerbated	3.5	1.1	1.1	2.5	0.8
Gastrointestinal or Vascular Events‡§	2.4	0.4	0.4	2.2	0.8
Gastrointestinal Events Present	2.1	0.0	0.4	1.9	0.6
Vascular Events Present‡	1.0	0.4	0.0	0.8	0.2
Other therapy-related event	1.1	0.7	0.7	0.3	0.0
Treatment-Unrelated	1.0	0.7	0.7	0.0	0.0

* Includes 1 patient who died on Day 62.
† Includes 1 patient who died on Day 82.
‡ Includes venous and/or arterial events and all instances of sudden death
§ Includes patients who had both cytotoxic and vascular events
Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin

2.3.3 Conclusions

The conclusions of the committee members are summarized below:

- Most deaths occurred in the first cycle of therapy, as has been noted in past experience with 5-FU/LV or irinotecan/5-FU/LV [Grem 1987, Poon 1989, Petrelli 1989, Buroker 1994, Gruia 1999, Miller 1999]
- The primary cause of drug-related death was sepsis in the context of diarrhea and neutropenia caused by chemotherapy-induced cytotoxicity to the gastrointestinal tract and bone marrow.
- A number of patients had fatal vascular events (both arterial and venous). These vascular events were considered by the committee to be potentially treatment-related, although a specific pharmacological reason for a cause and effect relationship between chemotherapy and these events was not evident.
- Close patient monitoring was not always routinely performed.
- Implementation of supportive care measures (particularly use of antibiotics) sometimes occurred late and antibiotic coverage was not always sufficiently broad.
- Dose modification measures could be improved.

2.3.4 Recommendations

The committee made the following recommendations:

- Oncologists should be advised of the possibility of fatal gastrointestinal and vascular events.
- The need for careful patient monitoring should be emphasized, particularly in the first-cycle of therapy.
- Early support with antibiotics (including use of an oral fluoroquinolone, as is common in Europe [Jacques 1997a, Jacques 1997b, Gruia 1999]) should be encouraged.
- Dose modification criteria should be modified consistent with important lessons learned during the development of the weekly Roswell Park 5-FU/LV regimen [Grem 1987, Petrelli 1989]. Specifically, rather than allowing chemotherapy treatment for patients with grade 1 or 2 diarrhea, dosing should be delayed until patients have been diarrhea-free for at least 24 hours.

3. REVIEW OF MORTALITY RATES IN THE THERAPY OF COLORECTAL CANCER

3.1 First-Line Therapy of Metastatic Colorectal Cancer

3.1.1 Background and Methods

As has already been noted, NCCTG investigators introduced the 60-day, all-cause death rate as a new method of assessing early mortality within a study. In most publications,

only investigator-described toxic deaths had been provided. Consequently, it was difficult to place the NCCTG mortality figures into context.

In order to provide a perspective from which to assess these types of early mortality results, Pharmacia has collated data from multiple trials assessing the use of 5-FU/LV or irinotecan/5-FU/LV. In order to be included in this review, studies were required to meet the following criteria:

- Trials had randomized, multicenter, phase II or phase III designs
- First-line therapy of metastatic colorectal cancer was studied
- 5-FU/LV or irinotecan/5-FU/LV combinations were evaluated
- Schedules of administration of 5-FU/LV included the Mayo Clinic, Roswell Park or de Gramont regimens
- Schedules of irinotecan/5-FU/LV included the Saltz or Douillard regimens
- Starting doses or 5-FU, LV, and irinotecan were those approved by the FDA or those currently employed in cooperative-group- or industry-sponsored studies

The search identified a representative number of both cooperative-group and industry-sponsored studies that met these criteria. Based on this selection, Pharmacia contacted the relevant cooperative groups (NCCTG, Eastern Cooperative Oncology Group [ECOG], Southwest Oncology Group [SWOG], German Study Group for the Palliative Treatment of Metastatic Colorectal Cancer, French Intergroup) and manufacturers (Aventis, Bristol-Myers-Squibb, Genentech, Roche, Sugen) in order to obtain mortality information from these studies. All of the contacted groups and companies graciously agreed to provide this information.

3.1.2 Results

Including Studies 0038 and V303, data from trials assessing standard methods of 5-FU/LV were made available. The most studied regimen was the Mayo Clinic method of administering 5-FU/LV; information on this regimen could be obtained from 8 trials (including Study 0038). This regimen has FDA regulatory sanction because it was used to approve LV. In addition, it has been the standard control arm for testing of new agents in the US, including irinotecan/5-FU/LV, capecitabine, and UFT. The Roswell Park method of weekly 5-FU/LV administration was also surveyed; data on this regimen were available from 6 trials. While this regimen has not been the basis for FDA regulatory action, it has been widely accepted as a community standard in certain regions of the US. Information regarding the de Gramont regimen has not been as thoroughly documented; data from only 3 trials (including V303) described the use of this regimen.

Information was also provided from trials further evaluating relevant irinotecan/5-FU/LV therapies (including Studies 0038, V303, and N9741). The most studied regimen was the Saltz method of administering irinotecan/5-FU/LV; information on this regimen could be obtained from 6 trials involving 927 patients. The Douillard method of irinotecan/5-FU/LV had been assessed in 5 trials involving 336 patients.

The 60-day, all-cause and investigator-reported, drug-related mortality rates from these studies are provided in Display 7.

Display 7. Sixty-day and Therapy-related Mortality by Regimen and Study in First-Line Therapy for Metastatic Colorectal Cancer – Cooperative Group and Industry-Sponsored Studies

Regimen Sponsor [Author (Study) Year]	N	60-Day, All-Cause Mortality		Therapy-Related Mortality (Investigator Assessment)	
		Rate, %	95% CI, %	Rate, %	95% CI, %
5-FU/LV					
Mayo Clinic Bolus 5-FU/LV					
Historical	**1593**	**6.5**	**4.1- 9.0**		
NCCTG [Poon 1989]	70	6.3	1.6-14.0	0.6	0.0- 5.1
NCCTG [Buroker 1994]	183	9.8	5.9-15.1	2.7	0.9- 6.3
SWOG [Leichman 1995]	85	4.6	1.3-11.6	2.4	0.3- 8.2
French Intergroup [de Gramont 1997]	216	8.0 *	4.7-12.3	NR	NA
Aventis [Graeven 2000]	50	6.0	1.3-16.5	4.0	0.5-13.7
Bristol-Myers-Squibb [Pazdur 1999]	396	5.3	3.3- 8.0	NR	NA
Roche [Hoff 2001]	593	6.2	4.4- 8.5	1.0 †	0.2- 2.9
Pharmacia (Study 0038)	***219***	***7.3***	***4.2-11.6***	1.4	0.3- 4.0
Overall	**1812**	**6.6**	**4.1- 9.2**		
Roswell Park Bolus 5-FU/LV					
GITSG [Petrelli 1989]	109	10.0 *	5.1-17.3	6.4	2.6-12.8
NCCTG [Buroker 1994]	179	13.4	8.8-19.3	1.1	0.1- 4.0
SWOG [Leichman 1995]	86	5.9	1.9-13.0	0.0	0.0- 4.2
German Study Group [Jäger 1996]	148	4.1	1.5- 8.6	NR	NA
ECOG [O'Dwyer 2001]	224	4.5	2.2- 8.1	1.3	0.3- 3.9
Sugen [SU5416-031 2001]	339	7.7	5.1-11.0	0.9	0.2- 2.6
Overall	**1085**	**7.6**	**4.1-11.1**		
de Gramont Infusional 5-FU/LV					
Historical	**253**	**5.5**	**2.3- 8.8**		
French Intergroup [de Gramont 1997]	217	6.0 *	3.2-10.0	NR	NA
Aventis [Labianca 2001]	36	2.7	0.1-14.5	0.0	0.0- 9.7
Aventis (Study V303)	***143***	***1.4***	***0.2- 5.0***	0.0	0.0- 2.5
Overall	**396**	**4.0**	**1.1- 6.9**		
Irinotecan/5-FU/LV					
Saltz Irinotecan/Bolus 5-FU/LV					
Post-registration	**702**	**3.8**	**1.3- 6.2**		
Aventis [Graeven 2000]	46	0.0	0.0- 7.7	0.0	0.0- 7.7
NCCTG [N9741 2001]	289	4.8	2.7- 8.0	NR	NA
Aventis [Ben Ayed 2001]	51	7.2	2.2-18.9	3.9	0.5-13.5
Sugen [SU5416-035 2001]	50	2.0	0.1-10.6	0.0	0.0- 7.1
Genentech [Anti-VEGF 2001]	266	3.0	1.3- 5.8	NR	NA
Pharmacia (Study 0038)	***225***	***6.7***	***3.8-10.8***	0.9	0.1- 3.2
Overall	**927**	**4.5**	**1.8- 7.2**		
Douillard Irinotecan/Infusional 5-FU/LV					
Post-registration‡	**191**	**2.6**	**0.0- 6.9**		
Aventis [Labianca 2001]	50	2.0	0.1-10.6	0.0	0.0 -7.1
Aventis [HK1.602 2001]	66	1.5	0.0- 8.2	0.0	0.0 -5.4
Aventis [Ben Ayed 2001]	53	3.8	0.5-13.0	1.9	0.0-10.1
Sugen [SU5416-035 2001]	22	4.5	0.1-22.8	4.5	0.0-22.8
RPR V303 (Aventis)	***145***	***2.1***	***0.4- 5.9***	0.7	0.0- 3.8
Overall‡	**336**	**2.4**	**0.0-5.5**		

Summary estimates (including 95%CIs) are computed using weighted averages of the individual study estimates and their standard deviations. Exact 95%CI were computed for the individual studies.

* Determined graphically from published Kaplan-Meier survival curve

† Includes 303 patients participating in 1 of 2 studies (Study SO14695)

‡ Includes patients treated with irinotecan/5-FU/LV alone and with anti-VEGF antibody/irinotecan/5-FU/LV

Abbreviations: 5-FU = 5-fluorouracil, CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, GITSG = Gastrointestinal Tumor Study Group, LV = leucovorin, NA = not applicable, NCCTG = North Central Cancer Treatment Group, NR = not reported, SWOG = Southwest Oncology Group

For the Mayo Clinic regimen, the historical results indicate an overall 60-day, all-cause mortality rate of 6.6 (95%CI: 4.1-9.2%). Parallel results are noted with the Roswell Park regimen with an overall 60-day mortality rate of 7.6% (95%CI: 4.1-11.1%). The 60-day mortality rates observed in Study 0038 with the Mayo Clinic 5-FU/LV (7.3%), and with the Saltz irinotecan/5-FU/LV in both Study 0038 (6.7%) and in Study N9741 (4.5%), appear to be quite consistent with these other results observed in trials of monthly or weekly 5-FU/LV bolus therapy.

Antecedent to its use in V303, only one large study of de Gramont 5-FU/LV was available [de Gramont 1997]. In this French Intergroup trial, the regimen was associated with a 60-day, mortality rate of 6.0% (95%CI: 3.2-10.0%). When combined with a smaller experience in 36 patients, the overall historical 60-day, all-cause mortality rate with the regimen was 5.5% (95%CI: 2.3-8.8%). The 60-day mortality rates observed in Study V303 with de Gramont 5-FU/LV (1.4%) and with Douillard irinotecan/5-FU/LV (2.1%) compare favorably with the amalgamated experience with de Gramont 5-FU/LV.

Also described in Display 7 are data from post-registration trials employing irinotecan/5-FU/LV regimens. If only these post-marketing studies (including N9741) are considered, the 60-day post-registration mortality experience with the Saltz irinotecan/5-FU/LV regimen is 3.8% (95%CI: 1.3-6.2%). Similarly, if only post-marketing studies are considered, the 60-day post-registration mortality experience with the Douillard irinotecan/5-FU/LV regimen is 2.6% (95%CI: 0.0-6.9%). These results with both the Saltz and Douillard regimens suggest post-marketing mortality rates that are as low as any observed in the past 5-FU/LV bolus or infusional experience.

A repeated pattern across the studies is that investigator-reported, drug-related mortality rates are consistently lower than the 60-day, all-cause mortality rates, emphasizing that cross-comparison of these 2 different types of mortality figures should be avoided.

3.2 Adjuvant Therapy of Surgically Resected Colon Cancer

3.2.1 Background and Methods

As was done in the metastatic setting, Pharmacia has collated mortality data from several trials assessing the use of 5-FU/LV or irinotecan/5-FU/LV as adjuvant therapy of colon cancer. With the exception that these trials focused on study of adjuvant chemotherapy, criteria for selection were the same as those employed in Section 3.1.

The search identified a small number of both cooperative-group and industry-sponsored studies that met these criteria, namely ECOG Study E2288 [Haller 1998], the National Surgical Adjuvant Breast and Bowel Project (NSABP) Study C-04 [Wolmark 1999], CALGB Study C89803 [C89803 2001] and Aventis Studies V307 (PETACC-3) [V307 2001] and Accord-2 [Accord-2 2001].

3.2.2 Results

The most studied regimen was the Roswell Park method of administering 5-FU/LV; data on this regimen could be obtained from 3 trials. One 4-arm study employed the Mayo Clinic regimen as one of its arms. For the de Gramont regimen, data from only one trial are available.

The 60-day, all-cause mortality rates from these studies are provided in Display 8.

Display 8. Sixty-day Mortality by Regimen and Study in Adjuvant Therapy of Surgically Resectable Colon Cancer – Cooperative Group and Industry-Sponsored Studies

Regimen Sponsor [Author (Study) Year]	N	60-Day, All-Cause Mortality	
		Rate, %	95% CI, %
5-FU/LV			
Mayo Clinic Bolus 5-FU/LV			
ECOG [Haller 1998]	953	0.52	0.17-1.22
Roswell Park Bolus 5-FU/LV			
NSABP [Wolmark 1999]	691	0.56 *	0.16-1.48
ECOG [Haller 1998]	946	0.85	0.37-1.66
CALGB [C89803 2001]	628	0.80	0.26-1.85
Overall	**2265**	**0.75**	0.14-1.35
de Gramont Infusional 5-FU/LV			
Aventis [V307 2001]	539	0.19	0.00-1.03
Aventis [ACCORD-2 2001]	127	0.00	0.00-2.86
Overall	**666**	**0.15**	0.00-0.51
Irinotecan/5-FU/LV			
Saltz Irinotecan/Bolus 5-FU/LV			
CALGB [C89803 2001]	635	2.36	1.33-3.87
Douillard Irinotecan/Infusional 5-FU/LV			
Aventis [V307 2001]	533	0.75	0.20-1.91
Aventis [ACCORD-2 2001]	127	0.00	0.00-2.86
Overall	**660**	**0.61**	0.00-1.32

Summary estimates (including 95%CIs) are computed using weighted averages of the individual study estimates and their standard deviations. Exact 95%CI were computed for the individual studies.
* Includes all on-treatment deaths
Abbreviations: 5-FU = 5-fluorouracil, CALGB = Cancer and Leukemia Group B, CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, LV = leucovorin, NSABP = National Surgical Breast and Bowel Project

In this context, the 60-day, all-cause mortality rate of 2.4% with Saltz irinotecan/5-FU/LV in Study C89803 is of concern. Given the prospect that adjuvant irinotecan/5-FU/LV therapy may offer substantial long-term disease-free and survival benefits, it will be particularly important to evaluate all patients for risk factors for early adverse outcomes and death in order to make sure that appropriate patient selection and supportive care can be instituted. The postoperative status of patients who have just undergone major intra-abdominal surgery may predispose patients receiving combination adjuvant therapy to adverse events that are not manifest in the metastatic setting. The potential influence of such problems as surgery-induced ileus, uncompensated loss of colonic absorptive surface, immobility, and hepatic effects of anesthesia have not been elucidated. Important assessments may include type and extent of surgery and anesthesia, duration of hospitalization; time between surgery and initiation of chemotherapy; and presence of baseline dehydration, malnutrition (eg, depressed albumin), functional compromise, and/or cardiovascular risk factors. Similarly, subpopulation analysis may identify patients at high risk of disease recurrence (eg, those with >4 positive lymph nodes, or cancer-related obstruction or perforation) who may derive particular tumor control benefit from irinotecan-based adjuvant treatment.

3.3 Conclusions

In the metastatic setting, it does not appear that either Saltz irinotecan/5-FU/LV or Douillard irinotecan/5-FU/LV subject patients to a greater risk of early death than do bolus or infusional regimens of 5-FU/LV that have been widely used in the past.

In the adjuvant setting, there must be concern regarding use of irinotecan/5-FU/LV chemotherapy until the results of Study C89803 are more fully analyzed. Pending availability of complete efficacy and safety data, adjuvant use of irinotecan/5-FU/LV should be considered experimental.

4. ANALYSIS OF RISK FACTORS FOR ADVERSE EVENTS

4.1.1 Background and Methods

As was noted by the independent review committee, its analysis was necessarily limited in scope because the members could only assess patient characteristics and clinical information for those patients who died during protocol treatment. Because the committee's analysis did not include patients who experienced severe, but non-lethal, toxicities or those who developed moderate, mild, or no toxicities, they could not develop a risk profile for those patients most likely to encounter varying degrees of toxicity while receiving treatment. In addition, the independent review panel was not able to review the balance of prognostic factors (eg, performance status or organ dysfunction) across the arms of the 2 studies or relative to other studies that would allow a full comparison of risk. Because Studies 0038 and V303 are completed and fully analyzed there is the opportunity to perform a retrospective review of these trials to discern which baseline factors might best signal clinicians that a patient is likely to have substantial risk of an adverse outcome.

In evaluating the likelihood of early adverse events by baseline patient characteristics, the focus of analysis has been on the most consequential clinical and laboratory adverse outcomes in patients who received the Saltz and Douillard irinotecan/5-FU/LV regimens in Studies 0038 and V303. The adverse outcomes are described in terms of several baseline characteristics (age, gender, performance status, prior adjuvant therapy, prior radiation therapy, serum LDH, SGOT [AST], total bilirubin, WBC, hemoglobin, and serum creatinine). These factors were systematically evaluated in both trials, are readily obtainable in clinical practice, and have potential bearing on drug disposition or may indicate a predilection for toxicity based on organ dysfunction. In addition, baseline performance status and the laboratory parameters have previously been identified as having prognostic significance for efficacy or safety in colorectal cancer [Kemeny 1989, Rougier 1995, Jacques 1997a, Jacques 1997b, Miller 1998a, Gruia 1999, Miller 1999, Knight 2000, Knight 2001]. Given the well-established observation that drug-related deaths occur in the first chemotherapy cycle [Grem 1987, Petrelli 1989, Rothenberg 2001], and the fact that this cycle is most critical in terms of establishing the most tolerable dose for each patient, particular emphasis is placed on first-cycle data.

The frequencies of early adverse events were segregated by the selected patient characteristics. For each event, statistical significance was assessed by logistic regression analysis with forward selection ($p<0.1$ for entry). All clinical and baseline variables were considered with the exception of prior radiation in Study 0038 and baseline serum

creatinine in Study V303 (each of which could not be adequately described because there were too few patients). In general, covariates were categorized dichotomously (eg, gender by male versus female or laboratory values by normal versus abnormal). Performance status was categorized as 0/1 versus 2. Given the inability to define any particular age groups as "young" or "old", age was included in the models as a continuous variable but described in terms of <65 versus ≥65 years of age since this had been a stratification factor in the conduct of Study 0038.

4.1.2 Results

4.1.2.1 Clinical Baseline Patient Characteristics

Display 9 and Display 10 (pages 22-23) provide an overview of early adverse outcomes by clinical patient characteristics. Statistical significance ($p \leq 0.05$, $p \leq 0.01$, or $p \leq 0.001$) in the logistic regression model is noted in red and with asterisks.

4.1.2.1.1 Performance Status

In Study 0038, the primary clinical adverse prognostic factor for early adverse events with Saltz irinotecan/5-FU/LV was consistently and repeatedly performance status, particularly performance status 2. Patients with poor performance status were significantly more likely to experience grade 3-4 vomiting ($p \leq 0.05$), neutropenic fever or infection ($p \leq 0.05$), or hospitalization ($p < 0.001$). Such patients were also significantly more likely to die within 30 days from the end of first-cycle therapy ($p < 0.05$) or within 60 days from the beginning of treatment ($p < 0.01$). The prospect that a patient with performance status 2 would not complete Cycle 1 of therapy was >50% ($p \leq 0.001$). When considering the combined incidence of any first-cycle neutropenic fever, hospitalization, discontinuation due to an adverse event, or death, patients with performance status 2 had a 66.7% likelihood of one of these adverse outcomes ($p \leq 0.001$).

Poor performance status was also documented to be a risk factor in Study V303 with Douillard irinotecan/5-FU/LV. Patients with performance status 2 had a 75% frequency of first-cycle hospitalization ($p \leq 0.01$). Patients with compromised performance status were more likely to experience neutropenic fever or infection, discontinue therapy due to an adverse event, die within 30 days of the end of first-cycle therapy (although these associations were not statistically significant) or fail to complete Cycle 1. When considering the combined incidence of any first-cycle neutropenic fever, hospitalization, discontinuation due to an adverse event, or death, patients with performance status 2 had a 83.3% likelihood of one of these adverse outcomes ($p \leq 0.001$).

Generally analogous findings were noted in patients receiving the Mayo Clinic and de Gramont 5-FU/LV regimens (eg, patients with performance status 2 were more likely to be hospitalized, to fail to complete Cycle 1 of therapy, or to die within 60 days from the beginning of treatment [Appendix A, Table 12]).

4.1.2.1.2 Other Clinical Parameters

For the Saltz and Douillard regimens, other clinical baseline factors were only variably or weakly associated with first-cycle adverse outcomes. For example, older age was significantly ($p \leq 0.05$) associated with a greater frequency of first-cycle neutropenic fever

in Study V303, but this was not confirmed in Study 0038 (despite the fact that Study 0038 had patients >75 years of age and Study V303 did not). The reliability of these results by age is not clear. In general, age ≥65 years has not been associated specifically with an altered pharmacokinetic profile or enhanced risk of neutropenia with single-agent irinotecan [Pazdur 1997, Schaaf 1997, Von Hoff 1997]. Similarly, there is evidence that the safety of 5-FU/LV in colon cancer therapy is not substantially altered by age [Sargent 2001].

In Study 0038, female gender was associated with a greater likelihood of grade 3-4 neutropenia ($p \leq 0.05$) but this was not corroborated in the analysis of grade 4 neutropenia in the same study or in the analyses of grade 3-4 or grade 4 neutropenia in Study V303 and thus no definite conclusions can be drawn.

Prior adjuvant therapy was associated with greater likelihood of grade 3-4 diarrhea ($p \leq 0.01$) in Study 0038; however, a similar association was not noted in Study V303. Such a correlation might be indicative of a depletion of gastrointestinal crypt cell reserve resulting from adjuvant cytotoxic treatment. However, such a hypothesis is not supported when considering bone marrow reserve; there was no significant impact of prior adjuvant therapy on neutrophil counts.

In Study V303, prior irradiation was significantly correlated with a greater frequency of grade 3-4 diarrhea. An association between prior radiation and an increased incidence of irinotecan-related diarrhea has been described in a phase II study assessing every-3-week, second-line, single-agent irinotecan administration [Mahjoubi 1994], but this correlation has not been observed in other trials with the every-3-week schedule [Jacques 1997a, Jacques 1997b, Miller 1998b] or with weekly treatment [Miller 1997, Pazdur 1997, Von Hoff 1997]. Too few patients with prior radiotherapy were enrolled to Study 0038 to draw meaningful conclusions from this study.

Display 9. Early Adverse Outcomes by Baseline Clinical Patient Characteristics for the Saltz Irinotecan/5-FU/LV Regimen – Study 0038 (Treated Populations)

Baseline Characteristic	First-Cycle Events												Death ≤60 days from First Therapy
	n	Grade 3-4 Diarrhea	Grade 3-4 Vomiting	Thrombo-embolism	Neutropenia		Neutro-penia with Fever or Infection†	Hospita-lizations‡	Disconti-nuations due to Adverse Events§	Deaths ≤30 days from Last Therapy¶	Combined Adverse Outcomes£	Failed to Complete Cycle 1¥	
					Grade 3-4	Grade 4							
Age (%)													
<65 years	137	12.4	4.4	1.5	38.0	16.8	9.5	23.4	2.2	4.4	28.5	16.1	6.6
≥65 years	88	13.6	9.1	4.6	47.7	22.7	18.2	42.1	4.5	6.8	45.5	21.6	6.8
Gender (%)													
Male	147	12.1	5.4	2.0	**37.4***	17.7	12.2	27.9	2.7	6.8	33.3	17.7	7.5
Female	78	14.1	7.7	3.9	**50.0**	21.8	14.1	35.9	3.8	2.6	38.5	19.2	5.1
Performance Status (%)													
0	87	9.2	**3.5***	0.0	41.4	14.9	**8.1***	**18.4*****	1.1	**1.2***	**19.5*****	**9.2*****	**1.2****
1	105	14.3	**5.7**	4.8	41.9	21.0	**14.3**	**31.4**	3.8	**5.7**	**38.1**	**15.2**	**5.7**
2	33	18.2	**15.2**	3.0	42.4	24.2	**21.2**	**60.6**	6.1	**15.2**	**66.7**	**51.5**	**24.2**
Prior Adjuvant Therapy (%)													
No	200	**11.0****	6.5	2.0	42.5	19.5	12.5	29.5	3.5	5.0	34.0	17.0	6.5
Yes	25	**28.0**	4.0	8.0	36.0	16.0	16.0	40.0	0.0	8.0	44.0	28.0	8.0
Prior Radiation (%)													
No	219	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Yes	6												
All Patients (%)	225	12.9	6.2	2.7	41.8	19.1	12.9	30.7	3.1	5.3	35.1	18.2	6.7

Statistical significance was assessed by logistic regression analysis with forward selection (p<0.1 for entry) and age as a continuous variable. All baseline variables (including laboratory variables noted in following display) were considered with the exception of prior radiation (which had too few patients to categorize). Significant differences are noted in red. Where applicable, severity was graded by NCI CTC, Version 1.0.

† Includes patients with simultaneous occurrence of grade 3-4 neutropenia or leucopenia with grade ≥2 fever or grade 3-4 bacterial or fungal infections or sepsis.

‡ Includes patients hospitalized for any cause (whether or not specifically related to toxic effects of study therapy). Patients hospitalized more than once are counted only once in this analysis.

§ Includes discontinuations due to adverse events of any type.

¶ Includes patients who only received first-cycle therapy and died within 30 days of the last administration of study treatment.

£ Includes patients with simultaneous occurrence of grade 3-4 neutropenia or leucopenia with grade ≥2 fever or grade 3-4 bacterial or fungal infections or sepsis; hospitalization for any cause (whether or not specifically related to toxic effects of study therapy); discontinuations due to adverse events of any type; and/or patients who only received first-cycle therapy and died within 30 days of the last administration of study treatment.

¥ Includes patients who did not enter Cycle 2.

* p≤0.05, ** p≤0.01, *** p≤0.001

Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin, ND = not done

Display 10. Early Adverse Outcomes by Baseline Clinical Patient Characteristics for the Douillard Irinotecan/5-FU/LV Regimen – Study V303 (Treated Populations)

Baseline Characteristic	First-Cycle Events												Death ≤60 days from First Therapy
	n	Grade 3-4 Diarrhea	Grade 3-4 Vomiting	Thrombo-embolism	Neutropenia		Neutro-penia with Fever or Infection†	Hospita-lizations‡	Disconti-nuations due to Adverse Events§	Deaths ≤30 days from Last Therapy¶	Combined Adverse Outcomes£	Failed to Complete Cycle 1¥	
					Grade 3-4	Grade 4							
Age (%)													
<65 years	92	4.4	1.1	7.6	19.6	2.2	**0.0***	23.9	1.1	2.2	23.9	13.0	2.2
≥65 years	53	7.6	0.0	7.6	30.2	9.4	**9.4**	22.6	5.7	1.9	28.3	15.1	1.9
Gender (%)													
Male	103	3.9	1.0	4.9	23.3	3.9	2.9	19.4	1.9	1.0	20.4	9.7	1.0
Female	42	9.5	0.0	14.3	23.8	7.1	4.8	33.3	4.8	4.8	38.1	23.8	4.8
Performance Status (%)													
0	68	2.9	0.0	8.8	26.5	5.9	1.5	**16.2*** **	1.5	0.0	**16.2*** **	5.9	0.0
1	65	7.7	1.5	4.6	20.0	4.6	4.6	**21.5**	3.1	3.1	**24.6**	16.9	3.1
2	12	8.3	0.0	16.7	25.0	0.0	8.3	**75.0**	8.3	8.3	**83.3**	41.7	8.3
Prior Adjuvant Therapy (%)													
No	107	5.6	0.9	7.5	22.4	2.8	3.7	24.3	1.9	2.8	26.2	15.0	2.8
Yes	38	5.3	0.0	7.9	26.3	10.5	2.6	21.1	5.3	0.0	23.7	10.5	0.0
Prior Radiation (%)													
No	115	**3.5***	0.9	7.8	22.6	5.2	3.5	20.9	2.6	2.6	23.5	15.7	2.6
Yes	30	**13.3**	0.0	6.7	26.7	3.3	3.3	33.3	3.3	0.0	33.3	6.7	0.0
All Patients (%)	225	5.5	0.7	7.6	23.4	4.8	3.4	23.4	2.8	2.1	25.5	13.8	2.1

Statistical significance was assessed by logistic regression analysis with forward selection (p<0.1 for entry) and age as a continuous variable. All baseline variables (including laboratory variables noted in following display) were considered with the exception of baseline serum LDH (which was not routinely collected in all patients) and baseline serum creatinine (which had too few patients to categorize). Significant differences are noted in red. Where applicable, severity was graded by NCI CTC, Version 1.0.

† Includes patients with simultaneous occurrence of grade 3-4 neutropenia or leucopenia with grade ≥2 fever or grade 3-4 bacterial or fungal infections or sepsis.

‡ Includes patients hospitalized for any cause (whether or not specifically related to toxic effects of study therapy). Patients hospitalized more than once are counted only once in this analysis.

§ Includes discontinuations due to adverse events of any type.

¶ Includes patients who only received first-cycle therapy and died within 30 days of the last administration of study treatment.

£ Includes patients with simultaneous occurrence of grade 3-4 neutropenia or leucopenia with grade ≥2 fever or grade 3-4 bacterial or fungal infections or sepsis; hospitalization for any cause (whether or not specifically related to toxic effects of study therapy); discontinuations due to adverse events of any type; and/or patients who only received first-cycle therapy and died within 30 days of the last administration of study treatment.

¥ Includes patients who did not enter Cycle 2.

* p≤0.05, ** p≤0.01, *** p≤0.001

Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin, ND = not done

4.1.2.2 Laboratory Baseline Patient Characteristics

Information regarding the influence of baseline laboratory abnormalities on the risk of adverse events is provided in Display 11 and Display 12 (pages 25-26). Statistical significance ($p \leq 0.05$, $p \leq 0.01$, or $p \leq 0.001$) in the logistic regression model is noted in red and with asterisks.

The exploration of associations between the baseline laboratory covariates and adverse events was generally inconclusive.

An increase in the risk of grade 4 neutropenia was observed in patients with abnormal bilirubin levels in Study 0038. Such an association has substantial pharmacological rationale. An association between serum bilirubin elevations and an increased frequency of neutropenia in irinotecan-treated patients has been noted in the past [Miller 1997,Von Hoff 1997, Wasserman 1997]. These clinical observations are supported by data from pharmacokinetic studies indicating reductions in clearance of irinotecan and increases in dose-normalized area under the curve (AUC_{0-24}) of its active metabolite, SN-38, in patients with elevated serum bilirubin values [Schaaf 2001, Venook 2001]. In Study V303, the small number of patients with elevated serum bilirubin levels precluded adequate evaluation.

Not surprisingly, an elevated WBC at baseline was associated with a lesser risk of grade 3-4 neutropenia in both studies ($p \leq 0.05$). There was no correlation with grade 4 neutropenia. In Study V303, abnormal hemoglobin was also correlated with grade 3-4 neutropenia. This latter finding was not observed in Study 0038.

An unexpected outcome was the association ($p \leq 0.01$) between abnormal creatinine and grade 4 neutropenia in Study 0038. The relevance of this finding is not clear since it is not significantly corroborated by any of the other analyses. In addition, the influence of creatinine on outcome could not be assessed in Study V303 because so few patients with abnormal creatinine were enrolled. An association between creatinine and toxicity has not been described in a recent comprehensive review of fluoropyrimidine clinical pharmacology [Grem 2001]. Renal elimination of 5-FU is quite low (≤15% of dose) and patients with kidney dysfunction do not require 5-FU dosage adjustments [Dorr 1994, Grem 2001]. Alterations in renal function would not be expected to have a major influence on irinotecan pharmacokinetics, since renal excretion does not represent a major route of elimination for irinotecan or SN-38 [Slatter 2000] and serum creatinine has not been correlated with irinotecan or SN-38 pharmacokinetic parameters in several trials [Chabot 1995, Schaaf 1995, Miya 2001, Venook 2001]. Thus, it appears unlikely that there is a pharmacokinetic basis for the observed association between serum creatinine and neutropenia experienced by patients receiving the irinotecan/5-FU/LV regimen in Study 0038.

The association in Study 0038 between a high WBC and failure to complete first-cycle therapy or death within 60 days of starting treatment is expected. Elevation in WBC at baseline is a significant prognostic factor for poor survival in Cox regression modeling [Knight 2000, Saltz 2000].

Display 11. Early Adverse Outcomes by Baseline Laboratory Patient Characteristics for the Saltz Irinotecan/5-FU/LV Regimen – Study 0038 (Treated Populations)

Baseline Characteristic	First-Cycle Events												Death ≤60 days from First Therapy
	n	Grade 3-4 Diarrhea	Grade 3-4 Vomiting	Thrombo-embolism	Neutropenia		Neutro-penia with Fever or Infection†	Hospita-lizations‡	Disconti-nuations due to Adverse Events§	Deaths ≤30 days from Last Therapy¶	Combined Adverse Outcomes£	Failed to Complete Cycle 1¥	
					Grade 3-4	Grade 4							
LDH (%)													
≤ULN	83	14.5	9.6	2.4	49.4	18.1	13.3	32.5	3.6	2.4	33.7	15.7	2.4
>ULN	126	11.1	4.0	2.4	36.5	19.1	11.1	27.8	2.4	7.1	34.1	19.1	9.5
SGOT (%)													
≤ULN	158	12.7	7.6	2.5	46.2	19.0	15.2	31.0	3.2	5.7	34.2	17.7	5.7
>ULN	63	11.1	1.6	3.2	33.3	20.6	7.9	28.6	3.2	4.8	36.5	19.1	9.5
Bilirubin (%)													
≤ULN	210	13.3	6.7	2.4	40.5	**17.6***	12.9	31.0	3.3	4.3	35.2	17.6	5.7
>ULN	15	6.7	0.0	6.7	60.0	**40.0**	13.3	25.7	0.0	20.0	33.3	26.7	20.0
WBC (%)													
<8 x10^3/mm^3	108	14.8	5.6	1.9	**50.0***	18.5	13.9	26.9	1.9	1.9	29.6	**11.1***	**1.9***
≥8 x10^3/mm^3	117	11.1	6.8	3.4	**34.2**	19.7	12.0	34.2	4.3	8.6	40.2	**24.8**	**11.1**
Hemoglobin (%)													
≥11g/dL	167	13.2	6.0	1.2	41.9	17.4	13.2	**27.5***	3.6	5.4	32.3	19.2	6.6
<11g/dL	58	12.2	6.9	6.9	41.4	24.1	12.1	**39.7**	1.7	5.2	43.1	15.5	6.9
Creatinine (%)													
≤ULN	209	13.4	5.7	2.9	40.7	**17.2****	12.9	31.1	2.9	4.8	35.4	17.7	6.2
>ULN	16	6.3	12.5	0.0	56.3	**43.8**	12.5	25.0	6.3	12.5	31.3	25.0	12.5
All Patients (%)	225	12.9	6.2	2.7	41.8	19.1	12.9	30.7	3.1	5.3	35.1	18.2	6.7

Statistical significance was assessed by logistic regression analysis with forward selection (p<0.1 for entry) and age as a continuous variable. All baseline variables (including clinical variables noted in preceding display) were considered with the exception of prior radiation (which had too few patients to categorize). Significant differences are noted in red. Where applicable, severity was graded by NCI CTC, Version 1.0.

† Includes patients with simultaneous occurrence of grade 3-4 neutropenia or leucopenia with grade ≥2 fever or grade 3-4 bacterial or fungal infections or sepsis.

‡ Includes patients hospitalized for any cause (whether or not specifically related to toxic effects of study therapy). Patients hospitalized more than once are counted only once in this analysis.

§ Includes discontinuations due to adverse events of any type.

¶ Includes patients who only received first-cycle therapy and died within 30 days of the last administration of study treatment.

£ Includes patients with simultaneous occurrence of grade 3-4 neutropenia or leucopenia with grade ≥2 fever or grade 3-4 bacterial or fungal infections or sepsis; hospitalization for any cause (whether or not specifically related to toxic effects of study therapy); discontinuations due to adverse events of any type; and/or patients who only received first-cycle therapy and died within 30 days of the last administration of study treatment.

¥ Includes patients who did not enter Cycle 2.

* p≤0.05, ** p≤0.01, *** p≤0.001

Abbreviations: 5-FU = 5-fluorouracil, LDH = lactate dehydrogenase, LV = leucovorin, SGOT = serum glutamate-oxalate transferase, ULN = upper limit of normal, WBC = white blood count

Display 12. Early Adverse Outcomes by Laboratory Patient Characteristics for the Douillard Irinotecan/5-FU/LV Regimen – Study V303 (Treated Populations)

Baseline Characteristic	First-Cycle Events												Death ≤60 days from First Therapy
	n	Grade 3-4 Diarrhea	Grade 3-4 Vomiting	Thrombo-embolism	Neutropenia		Neutro-penia with Fever or Infection†	Hospita-lizations‡	Disconti-nuations due to Adverse Events§	Deaths ≤30 days from Last Therapy¶	Combined Adverse Outcomes£	Failed to Complete Cycle 1¥	
					Grade 3-4	Grade 4							
LDH (%)													
≤ULN	64	3.1	0.0	6.3	21.9	6.3	3.1	20.3	4.7	0.0	23.4	10.9	0.0
>ULN	44	11.4	0.0	11.4	30.0	6.8	6.8	30.0	0.0	4.6	31.8	15.9	4.6
SGOT (%)													
≤ULN	109	5.5	0.9	6.4	25.7	6.4	4.6	22.9	3.7	0.9	25.7	12.8	0.9
>ULN	30	3.3	0.0	6.7	13.3	0.0	0.0	20.0	0.0	0.0	20.0	10.0	0.0
Bilirubin (%)													
≤ULN	102	6.0	0.8	6.7	23.9	5.2	3.7	22.4	2.2	2.2	24.6	13.4	2.2
>ULN	9	0.0	0.0	18.2	18.2	0.0	0.0	36.4	9.1	0.0	36.4	18.2	0.0
WBC (%)													
<8 x10^3/mm^3	75	4.0	1.3	6.7	**32.0****	8.0	4.0	17.3	2.7	0.0	21.3	10.7	0.0
≥8 x10^3/mm^3	70	7.1	0.0	8.6	**14.3**	1.4	2.9	30.0	2.9	4.3	30.0	17.1	4.3
Hemoglobin (%)													
≥11g/dL	120	5.8	0.8	7.5	**20.8***	5.0	2.5	22.5	3.3	1.7	25.0	14.2	1.7
<11g/dL	25	4.0	0.0	8.0	**36.0**	4.0	8.0	28.0	0.0	4.0	28.0	12.0	4.0
Creatinine (%)													
≤ULN	140	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
>ULN	5												
All Patients (%)	145	5.5	0.7	7.6	23.4	4.8	3.4	23.4	2.8	2.1	25.5	13.8	2.1

Statistical significance was assessed by logistic regression analysis with forward selection (p<0.1 for entry) and age as a continuous variable. All baseline variables (including clinical variables noted in preceding display) were considered with the exception of baseline serum LDH (which was not routinely collected in all patients) and baseline serum creatinine (which had too few patients to categorize). Significant differences are noted in red. Where applicable, severity was graded by NCI CTC, Version 1.0.

† Includes patients with simultaneous occurrence of grade 3-4 neutropenia or leucopenia with grade ≥2 fever or grade 3-4 bacterial or fungal infections or sepsis.

‡ Includes patients hospitalized for any cause (whether or not specifically related to toxic effects of study therapy). Patients hospitalized more than once are counted only once in this analysis.

§ Includes discontinuations due to adverse events of any type.

¶ Includes patients who only received first-cycle therapy and died within 30 days of the last administration of study treatment.

£ Includes patients with simultaneous occurrence of grade 3-4 neutropenia or leucopenia with grade ≥2 fever or grade 3-4 bacterial or fungal infections or sepsis; hospitalization for any cause (whether or not specifically related to toxic effects of study therapy); discontinuations due to adverse events of any type; and/or patients who only received first-cycle therapy and died within 30 days of the last administration of study treatment.

¥ Includes patients who did not enter Cycle 2.

* p≤0.05, ** p≤0.01, *** p≤0.001

Abbreviations: 5-FU = 5-fluorouracil, LDH = lactate dehydrogenase, LV = leucovorin, SGOT = serum glutamate-oxalate transferase, ULN = upper limit of normal, WBC = white blood count

4.1.3 Conclusions

Analysis of early adverse outcomes by patient risk factors indicates that a performance status of ≥2 is associated with a high likelihood of early adverse outcomes with either Saltz irinotecan/5-FU/LV or Douillard irinotecan/5-FU/LV. When coupled with low expectations that such patients will experience positive efficacy outcomes, it is clear that patients with poor performance status should only be considered for chemotherapy after a full discussion of the substantial potential for early toxicity and relative lack of clinical benefit.

Such findings are not unique to colon cancer. Recent experience in the combination therapy of both small cell and non-small cell lung cancers has indicated that patients with performance status 2 are at substantially greater risk for adverse outcomes and death [Johnson 1999, Ohe 1999, Kelly 2001] and that such patients may not be appropriate candidates for phase III studies [Johnson 1999].

Besides performance status, no other clinical factors were good predictors of adverse events. When adjusted for performance status and other prognostic indicators, older age was not clearly a risk for greater toxicity. While stratification of patients by age <65 or ≥65 years has been conventional in order to balance populations within studies, restrictions on therapy by age are difficult given the continuous nature of this variable and the lack of close correlation between age and physiologic status.

The small number of patients with elevated bilirubin enrolled to Study 0038 and especially to Study V303 precluded adequate evaluation of this laboratory abnormality as a risk factor for adverse outcomes. There is strong pharmacological rationale supporting decreased clearance of irinotecan and its metabolites with consequent enhancement of severe neutropenia in patients with hyperbilirubinemia [Miller 1997,Von Hoff 1997, Wasserman 1997, Schaaf 2001, Venook 2001]. In addition, elevated serum bilirubin is an adverse prognostic factor for early death due to progressive disease; in Cox regression models it has been identified as an independent prognostic indicator for shortened TTP and survival [Miller 1999, Knight 2000]. The clinical correlation of higher bilirubin with grade 3-4 neutropenia has been documented in the Camptosar package insert [Miller 1997].

5. OVERALL CONCLUSIONS AND IMPLICATIONS

Based on an assessment of mortality rates in the NCCTG and CALGB studies in the context of existing data from the phase III registration trials and other studies, and a retrospective analysis of risk factors for adverse outcome, Pharmacia believes that the following conclusions can be drawn:

1. The large phase III multicenter trials that were the basis for registration (Studies 0038 and V303) remain the only completed adequate and well-controlled studies available for review. These trials address important concepts regarding the efficacy and safety of the combination of irinotecan with each of the 2 commonly employed methods of 5-FU/LV administration (bolus and infusional therapy) in the regions of the world where these methods are most commonly used. Each of these studies independently documents that combining irinotecan with 5-FU/LV can benefit patients with metastatic colorectal cancer by inducing tumor shrinkage and extending tumor

control, and that these outcomes are associated with significantly prolonged life while maintaining quality of life. Analyses of important safety variables within each of Studies 0038 and V303 indicated that irinotecan can be added to 5-FU/LV and retain acceptable safety relative to a previous reference standard. In particular, both studies documented that the Saltz and Douillard combinations of irinotecan/5-FU/LV were not associated with higher mortality rates than were observed in randomized, concurrently treated control patients receiving reference 5-FU/LV regimens with widely acknowledged toxicity profiles.

2. It cannot be assumed from cross-study comparisons that the gastrointestinal and hematologic toxicity profiles observed with the Douillard regimen are better than those observed with the Saltz regimen. Such comparisons are particularly inappropriate given differences in baseline characteristics indicating that higher proportions of patients enrolled to Study 0038 had more compromised performance status and organ function. In view of the lack of experience with the Douillard regimen in the US, it seems premature to assume that the infusional regimen should be universally preferred. Given the complexity, patient inconvenience, and expense associated with infusional regimens, the relatively simple weekly Saltz irinotecan/bolus 5-FU/LV treatment paradigm may offer a better basis for addition of certain types of new therapies.

3. The 60-day, all-cause mortality rate in NCCTG Study N9741 that sparked the concern regarding the Saltz irinotecan/5-FU/LV regimen has proved not to be different from those already established in Studies 0038 and V303. Moreover, the 60-day, all-cause mortality rates from these 3 studies (Studies 0038, V303, and N9741) are no different from those associated with the use of 5-FU/LV in the first-line treatment of metastatic colorectal cancer. Available data from post-marketing trials employing the Saltz and Douillard irinotecan/5-FU/LV regimens document early mortality rates that continue to be as low as any attained in prior studies with 5-FU/LV when used as therapy of metastatic disease.

4. First-line therapy with combination irinotecan/5-FU/LV for metastatic disease is preferable to a sequence of first-line 5-FU/LV followed by second-line irinotecan. The 60-day, all-cause mortality documented for 5-FU/LV is not increased when concurrent irinotecan is added. Thus, reverting to a sequence of 5-FU/LV alone followed by irinotecan will not protect patients who are at risk from early treatment- or disease-related mortality, and it will deny improved tumor control and survival benefits to many patients. This conclusion is emphasized by the fact that the survival benefits associated with irinotecan/5-FU/LV therapy were achieved even though most patients treated with first-line 5-FU/LV in Studies 0038 and V303 received second-line irinotecan- and/or oxaliplatin-containing therapy.

5. As was indicated by the independent review committee, the cytotoxic (gastrointestinal) syndrome observed in patients treated on Study N9741 has been long recognized as a complication of 5-FU/LV regimens. The addition of irinotecan to 5-FU/LV can increase gastrointestinal adverse events (as documented in both Studies 0038 and V303). However, the frequency of deaths among patients with the gastrointestinal syndrome on Study N9741 was not different from the frequencies observed in Study 0038 with the Saltz regimen, in Study V303 with the Douillard

regimen, or with Roswell Park 5-FU/LV alone [Petrelli 1989]. Recommendations for amelioration of potentially life-threatening gastrointestinal toxicity with irinotecan/5-FU/LV made by the independent review committee in 2001 [Rothenberg 2001] serve to reinforce similar recommendations for 5-FU/LV alone already proposed by a similar group in 1989 [Grem 1987, Petrelli 1989].

6. The independent review committee has also advanced the concept of a vascular syndrome as a potential cause of chemotherapy-related mortality. While such an association has previously been documented (eg, in the adjuvant therapy of breast cancer [Levine 1988]), a pharmacological basis for a potential relationship to chemotherapy remains unclear. Given the lack of evidence for increased vascular mortality with irinotecan/5-FU/LV when given for metastatic colorectal cancer, no specific change in treatment practice can be advocated at this time, but it is reasonable that the potential for such events is documented in Camptosar labeling.

7. The data from Studies 0038 and V303 clearly establish that poor performance status is a substantial risk factor for serious early adverse outcomes. Patients described as having performance status 2 were more likely to experience first-cycle grade 3-4 vomiting, neutropenic fever or infection, hospitalization, discontinuations due to adverse events, or death. When coupled with the relative lack of therapeutic benefit, these safety data suggest that patients with poor performance status may not do well with irinotecan/5-FU/LV or any chemotherapy. Practitioners electing to treat such patients should do so only with considerable caution.

8. Pharmacia recognizes with concern that there was an imbalance in the number of early deaths on CALGB 89803 when comparing the irinotecan/5-FU/LV and 5-FU/LV arms of the study. Given the differences in susceptibility to toxicities that may exist between the adjuvant and metastatic treatment settings, it is difficult to know how to place these data into the context of the currently approved indication. With further evaluation, it may be possible to establish a profile for patients who are at particularly high risk for early chemotherapy-related mortality in the post-surgical adjuvant setting. Conversely, it may be possible to establish a population of patients who are at particularly high risk for disease recurrence and who may obtain considerable benefit from irinotecan-based adjuvant treatment. Only when these data are available will it be possible to provide a thorough understanding of the balance of the short-term risks and the long-term benefits of irinotecan/5-FU/LV as treatment for patients with surgically resected colon cancer. The use of irinotecan/5-FU/LV in the adjuvant setting remains outside of Camptosar product labeling; therefore, Pharmacia would propose no specific further actions related to the existing findings in this study at this time.

6. PROPOSED PACKAGE INSERT CHANGES

The information derived from the independent review committee report and this review of data from the pivotal registration trials do not change the positive assessments of benefit and risk already presented to FDA and ODAC in the 1999 sNDA in support of approval of the Saltz and Douillard irinotecan/5-FU/LV combinations. However, this re-examination does offer the opportunity to strengthen the Camptosar package insert such that Pharmacia can provide enhanced education about the benefits and risks of both the Saltz and Douillard irinotecan/5-FU/LV combinations in the first-line therapy of metastatic colorectal cancer. Based on these re-evaluations, Pharmacia is proposing the following changes to the package insert (see Appendix C for current package insert):

6.1 Black Box

- Inclusion of life-threatening infection as a potential complication of chemotherapy-related diarrhea.
- Emphasis on the need for antibiotic therapy in patients with severe diarrhea who are hospitalized for colitis/ileus, fever, or neutropenia.

6.2 Warnings, Precautions, and Patient Instructions

- Warning that patients with performance status 2 are at particular risk for early adverse outcomes and that physicians electing to treat patients with performance status 2 should inform such patients of the substantial potential for severe adverse events
- Re-emphasis that patients with a performance status of 3 or 4 should not be treated with irinotecan/5-FU/LV
- Documentation that life-threatening infection is a potential complication of chemotherapy-related diarrhea.
- Documentation that thromboembolic events have occurred in patients receiving irinotecan-containing therapy.
- Instructions that, in addition to loperamide, patients should be provided with a prescription for an oral fluoroquinolone antibiotic; that patients should fill this prescription and begin fluoroquinolone therapy if they develop diarrhea lasting >24 hours despite loperamide, diarrhea with fever, or diarrhea with neutropenia; and that patients with colitis/ileus, neutropenic fever or infection should be hospitalized promptly for intravenous antibiotic therapy.
- Increased emphasis that patients should contact their physician or nurse if they experience diarrhea for the first time during treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; an inability to take liquids by mouth due to nausea and vomiting; or an inability to get diarrhea under control with loperamide within 24 hours.

6.3 Adverse Reactions

- Insertion of a tabular summary of mortality rates for Studies 0038 and V303. Rates to be included would describe deaths within 60-days of first dose, deaths within 30 days

of last dose, deaths in association with cytotoxic and vascular events, and investigator-described, drug-related deaths.

6.4 Dosage and Administration

- Advisory statement regarding the need for close monitoring, especially during the first cycle of therapy.
- Recommendation that patients experiencing any grade of diarrhea within 24 hours prior to treatment administration should have treatment delayed until recovery of diarrhea to grade 0.

7. REFERENCES

The following references are cited in this document. Where both study reports and publications or supporting documents are available that describe the data, the publication or supporting references are printed in italics:

Accord-2. Phase III randomized open-label trial of 5-FU/FA with and without CPT-11 as adjuvant treatment for III high-risk colon cancer. Aventis, 2001 (ongoing study).

André T, Bensmaine MA, Louvet C, et al. Multicenter phase II study of bimonthly high-dose leucovorin, fluorouracil infusion, and oxaliplatin for metastatic colorectal cancer resistant to the same leucovorin and fluorouracil regimen. J Clin Oncol 17:3560-3568, 1999.

Anti-VEGF antibody. A phase III, randomized, placebo-controlled study comparing the combination of irinotecan/5-fluorouracil/ leucovorin with or without anti-VEGF antibody as first-line therapy of patients with advanced colorectal cancer. Genentech, 2001 (ongoing study).

Ben Ayed F, Khalfallah S, Tujakowski J, et al. CPT-11 combined or alternating with 5-fluororuracil/folinic acid (5-FU/FA) in advanced colorectal cancer (CRC). Proc Amer Soc Clin Oncol 20:135a [#536], 2001.

Blanc CH, Cote C, Guilloux E, Awad L. Open-label confirmatory multicentre phase II study of irinotecan hydrochloride (CPT-11) in patients with 5-FU-resistant colorectal cancer (Study number: RP 64174A-V-222). Bellon Rhône-Poulenc Rorer Technical Report, 1996.

Van Cutsem E, Rougier P, Droz JP, et al. Clinical benefit of irinotecan (CPT-11) in metastatic colorectal cancer resistant to 5-FU. Proc Am Soc Clin Oncol 16:268a, 1997.

Buroker TR, O'Connell MJ, Wieand HS, et al. Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of advanced colorectal cancer. J Clin Oncol 12(1):14-20, 1994.

C89803. Phase III intergroup trial of irinotecan (CPT-11) plus fluorouracil/leucovorin versus fluorouracil/leucovorin alone after curative resection for patients with stage III colon cancer. CALGB 2001 (ongoing study).

Chabot GG, Abigerges D, Catimel G et al. Population pharmacokinetics and pharmacodynamics of irinotecan (CPT-11) and active metabolite SN-38 during Phase I trials. Ann Oncol 6:141-51, 1995.

de Gramont A, Bosset JF, Milan C et al. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: A French intergroup study. J Clin Oncol 15(2):808-15, 1997.

Dietz AJ, Von Hoff DD, Elfring GL, Albert DG, Miller LL. A phase II study of irinotecan hydrochloride (CPT-11) in metastatic colorectal carcinoma refractory to previous 5-fluorouracil (5-FU)-based chemotherapy (protocol M/6475/0001). Upjohn Technical Report 7216-95-007, 1995a.

Rothenberg ML, Eckardt JR, Kuhn JG, Burris HA 3rd, Nelson J, Hilsenbeck SG, et al. Phase II trial of irinotecan in patients with progressive or rapidly recurrent colorectal cancer. J Clin Oncol 14(4):1128-35, 1996.

Dietz AJ, Von Hoff DD, Ragual RJ, Miller LL. A multicenter, phase II study of irinotecan hydrochloride (CPT-11) in metastatic colorectal carcinoma refractory to previous 5-fluorouracil (5-FU)-based chemotherapy (protocol M/6475/0003R). Upjohn Technical Report 7216-95-008, 1995b.

Pitot HC, Wender DB, O'Connell MJ, , et al. Phase II trial of irinotecan in patients with metastatic colorectal carcinoma. J Clin Oncol 15(8):2910-19, 1997.

Dietz AJ, Von Hoff DD, Elfring GL, Albert DG, Wolf DL, Locker PK, et al. A multicenter, open-label, phase II study of irinotecan hydrochloride (CPT-11) in patients with 5-fluorouracil (5-FU)-refractory colorectal cancer (protocol M/6475/0006). Upjohn Technical Report 7216-95-010, 1995c.

Rothenberg ML, Cox JV, DeVore RF, Hainsworth JD, Pazdur R, Rivkin SE, et al. A multicenter, phase II trial of weekly irinotecan (CPT-11) in patients with previously treated colorectal carcinoma. Cancer 85(4):786-95, 1999.

Dietz AJ, Von Hoff DD, Ragual RJ, Miller LL. A multicenter, phase II study of irinotecan hydrochloride (CPT-11) in metastatic colorectal carcinoma not previously treated with systemic chemotherapy (protocol M/6475/0003N). Upjohn Technical Report 7216-95-015, 1995d.

Pitot HC, Wender DB, O'Connell MJ, et al. Phase II trial of irinotecan in patients with metastatic colorectal carcinoma. J Clin Oncol 15(8):2910-19, 1997.

Dietz AJ, Von Hoff DD, Albert DG, Wolf DL, Locker PK, Miller LL. A phase II, open-label study of irinotecan hydrochloride (CPT-11) in patients with metastatic colorectal cancer not previously treated with chemotherapy or radiotherapy (protocol M/6475/0010). Upjohn Technical Report 7216-95-012, 1995e.

Conti JA, Kemeny NE, Saltz LB, Huang Y, Tong WP, Chou TC, et al. Irinotecan is an active agent in untreated patients with metastatic colorectal cancer. J Clin Oncol 14(3):709-15, 1996.

Dorr RT, Von Hoff DD. Cancer Chemotherapy Handbook, 2nd edition. Appleton & Lange, East Norwalk, CT, pp. 500-514, 1994.

Grem J, Shoemaker L, Petrelli N, et al. Severe life-threatening toxicities observed in a study using leucovroin with 5-FU. J Clin Oncol 10:1704, 1987 (letter).

Grem JL. 5-Fluoropyrimidines. In: Cancer Chemotherapy & Biotherapy: Principles & Practice, 3rd edition. Chabner BA, Longo DL, eds. Lippincott Williams & Wilkins, Philadelphia, pp. 185-264, 2001.

Gruia G. A randomized phase III multicentre trial comparing irinotecan hydrochloride trihydrate (CPT-11) in combination with 5-FU 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 (study number RP64174V-303). Rhône-Poulenc Rorer Final Study Report, 1999.

Douillard JY, Cunningham D, Roth AD et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 355:1041-1047, 2000 [Erratum, Lancet 355:1372, 2000].

Graeven U, Ridwelski K, Manns M, et al. Irinotecan (CPT-11) with bolus 5-fluorouracil (5-FU) and folinic acid (FA) in patients with previously untreated metastatic colorectal cancer (MCRC): An active and safe regimen. Proc Amer Soc Clin Oncol 19:246a [#952], 2000.

Haller DG, Catalano PJ, MacDonald JS, et al. Fluorouracil (FU), leucovorin (LV), and levamisole (LEV) adjuvant therapy for colon cancer: five-year final report of INT-0089. Proc Amer Soc Clin Oncol 17:256a [#982], 1998.

HK1.602. Combination chemotherapy with CPT-11, 5FU and leucovorin in the management of Chinese patients with metastatic colorectal cancer: a phase II study. Aventis, 2001 (ongoing study).

Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III trial. J Clin Oncol 19(8):2282-2292, 2001.

Jacques C. 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 (study number RP64174V-301). Rhône-Poulenc Rorer Final Study Report, 1997a.

Cunningham D, Pyrhonen S, James RD, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 352:1413-8, 1998.

Cunningham D; Glimelius B. A phase III study of irinotecan (CPT-11) versus best supportive care in patients with metastatic colorectal cancer who have failed 5-FU therapy. V301 Study Group. Semin Oncol 26(1 Suppl 5):6-12, 1999.

Jacques C, Rougier P, Bleiberg H. 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 (study number RP64174V-302). Rhône-Poulenc Rorer Final Study Report, 1997b.

Rougier P, Van Cutsem E, Bajetta E, et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 352:1407-12, 1998.

Van Cutsem E; Blijham GH. Irinotecan versus infusional 5-fluorouracil: a phase III study in metastatic colorectal cancer following failure on first-line 5-fluorouracil. V302 Study Group. Semin Oncol; 26(1 Suppl 5):13-20, 1999

Van Cutsem E, Rougier P, Droz JP et al. Clinical benefit of irinotecan (CPT-11) in metastatic colorectal cancer (CRC) resistant to 5-FU. Proc Am Soc Clin Oncol 16:[#950], 1997.

Jäger E, Heike M, Bernhard H, et al. Weekly high-dose leucovorin versus low-dose leucovorin combine with fluorouracil in advance colorectal cancer: Results of a randomized multicenter trial. J Clin Oncol 14(8):2274-5, 1996.

Johnson DH, Zhu J, Schiller J et al. E1594 – A randomized phase III trial in metastatic non-small cell lung cancer (NSCLC) – outcome of PS2 Patients (pts): An Eastern Cooperative Group (ECOG) trial. Proc Am Soc Clin Oncol 18:461a [#1779], 1999.

Kelly K, Lovato L, Bunn PA, et al. Cisplatin, etoposide, and paclitaxel with granulocyte colony-stimulating factor in untreated patients with extensive-stage small cell lung cancer: a phase II trial of the Southwest Oncology Group. Clin Cancer Res 7:2325-2329, 2001.

Kemeny N, Niedzwiecki D, Shurgot B, Oderman P. Prognostic variables in patients with hepatic metastases from colorectal cancer. Importance of medical assessment of liver involvement. Cancer 63:742-7, 1989.

Knight RD, Miller LL, Pirotta N, et al. First-line irinotecan (C), fluorouracil (F), leucovorin (L) especially improves survival (OS) in metastatic colorectal (MCRC) patients (pts) with favorable prognostic indicators. Proc Am Soc Clin Oncol 19:255a [#991], 2000.

Knight RD, Miller LL, Elfring GL, Pirotta N, Locker PK, Saltz LB. Evaluation of age, gender, performance status (PS), and organ dysfunction as predictors of toxicity with first-line irinotecan (C), fluorouracil (F), leucovorin (L) therapy of metastatic colorectal cancer (MCRC). Proc Amer Soc Clin Oncol 20:220a [#534], 2001.

Köhne CH, Schöffski P, Wilke H et al. Effective biomodulation by leucovorin of high-dose infusion fluorouracil given as a weekly 24-hour infusion: Results of a randomized trial in patients with advanced colorectal cancer. J Clin Oncol 16(2):418-26, 1998.

Labianca R, Martoni A, Galligioni E, et al. CPT-11 alternated with leucovorin + 5-fluorouracil (LV/5-FU2 regimen) in advanced colorectal cancer (ACC): a multicentric randomized phase II trial. Proc Amer Soc Clin Oncol 20:135a [#535], 2001.

Leichman CG, Fleming TR, Muggia FM, et al. Phase II study of fluorouracil and its modulation in advanced colorectal cancer: A Southwest Oncology Group Study. J Clin Oncol, 13(6):1303-11, 1995.

Levine MN, Gent M, Hirsch J, et al. The thrombogenic effect of anticancer therapy in women with stage II breast cancer. New Engl J Med 318:404-7, 1988.

Mahjaoubi M, Essermeant S. A multicenteric, open-label phase II trial with irinotecan-hydrochloride (CPT-11) in patients with inoperable advanced colorectal cancer previously treated or not with adjuvant or palliative 5-FU-based chemotherapy (study number CPT 205). Bellon Rhône-Poulenc Rorer Technical Report, 1994.

Armand JP, Ducreux M, Mahjoubi M, et al. CPT-11 (irinotecan) in the treatment of colorectal cancer. Eur J Cancer 31:1283, 1995.

Rougier P, Bugat R. CPT-11 in the treatment of colorectal cancer: clinical efficacy and safety profile. Semin Oncol 23(1 suppl 3):34-41, 1996.

Rougier P, Bugat R, Douillard JY, et al. Phase II study of irinotecan in the treatment of advanced colorectal cancer in chemotherapy-naive patients and patients pretreated with fluorouracil-based chemotherapy. J Clin Oncol 15:251-60, 1997.

Mery-Mignard D, Vernillet L. Phase I/II study of irinotecan in combination with 5FU + folinic acid according to the LV5FU2 regimen, in patients with pretreated metastatic colorectal carcinoma. Aventis Study Report RPR64174F-106, 1999.

Ducreux M, Ychou M, Seitz J-F, et al. Irinotecan combined with bolus fluorouracil, continuous infusion fluorouracil, and high-dose leucovorin every two weeks (LV5FU2 regimen): a clinical dose-finding and pharmacokinetic study in patients with pretreated metastatic colorectal cancer. J Clin Oncol 17(9):2901-8, 1999.

Miller LL, Elfring G. Influence of baseline serum bilirubin level on the likelihood of grade 3/4 neutropenia during Camptosar™ (irinotecan, CPT-11) therapy for previously treated colorectal cancer. Pivotal trials data update supporting change in package insert. Submitted to the FDA 29 September 1997. Pharmacia & Upjohn Study Report a0017476, 19 November 1997.

Miller LL, Petit RG, Elfring GL. Evaluation of carcinoembryonic antigen (CEA) levels during CPT-11 treatment of patients with previously treated colorectal cancer. Proc Am Soc Clin Oncol 17:297a [#1145], 1998a.

Miller LL, Elfring GL, Locker PK, Schaaf LJ, Walker J, Compton LD. Oncologic Drugs Advisory Committee brochure supporting full approval of CAMPTOSAR™ Injection (irinotecan hydrochloride injection), NDA #20-571, Supplement #8, September 1998b.

Miller LL, Pirotta N, Locker PK, Elfring GL. Irinotecan HCl: A phase III, randomized, controlled clinical trial of irinotecan HCl (CPT-11) alone, combined irinotecan HCl and 5-fluorouracil plus leucovorin, and 5-fluorouracil plus leucovorin alone in patients with untreated metastatic colorectal cancer (protocol M/6475/0038). Pharmacia & Upjohn Study Report a0057133, 1999.

Miller LL, Pirotta N, Locker PK, Elfring GL. Survival Update. Addendum to Clinical Study Reports: Study Report a0057133 for Protocol M/6475/0038 – Irinotecan HCl: A phase III, randomized, controlled clinical trial of irinotecan HCl (CPT-11) alone, combined irinotecan HCl and 5-fluorouracil plus leucovorin, and 5-fluorouracil plus leucovorin alone in patients with untreated metastatic colorectal cancer; and Study Report a0056073 for protocol RP64174V – 303: A randomised phase III multicentre trial comparing irinotecan hydrochloride trihydrate (CPT-11) in combination with 5-FU and folinic acid (5-FU/FA) to the same schedule of 5-FU/FA in the first-line palliative chemotherapy of patients with metastatic colorectal cancer, Pharmacia & Upjohn Study Report a0067163, January 2000.

Saltz LB, Cox JV, Blanke C et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 343:905-914, 2000.

Miya T, Goya T, Fujii H et al. Factors affecting the pharmacokinetics of CPT-11: the body mass index, age and sex are independent predictors of pharmacokinetic parameters of CPT-11. Invest New Drugs 19:61-7, 2001.

Morton RF, Goldberg RM, Sargent DJ, et al. Oxaliplatin or CPT-11 combined with 5FU/Leucovorin in advanced colorectal cancer: a NCCTG/CALGB study. Proc Am Soc Clin Oncol 20:125a, 2001.

N9741. A randomized phase III trial of two different regimens of CPT-11 plus 5-fluorouracil and leucovorin, two different regimens of oxaliplatin plus 5-fluorouracil and leucovorin and one regimen of oxaliplatin and CPT-11, compared to 5-fluorouracil and leucovorin as initial treatment of patients with advanced adenocarcinoma of the colon and rectum. NCCTG, 2001 (ongoing study).

O'Dwyer PJ, Manola J, Valone FH, et al. Fluorouracil modulation in colorectal cancer: lack of improvement with n-phosphonoacetyl-l-aspartic acid or oral leucovorin or interferon, but enhanced therapeutic index with weekly 24-hour infusion schedule – an Eastern Cooperative Oncology Group/Cancer And Leukemia Group B study. J Clin Oncol 19(9):2413-2421, 2001.

Ohe Y, Yamamoto S, Suzuki K, et al. Risk factors of treatment-related death (TRD) in chemotherapy (CT) and thoracic radiotherapy (TRT) for lung cancer. Proc Am Soc Clin Oncol 18:465a [#1795] 1999.

Pazdur R, Zinner R, Rothenberg ML, et al. Age as a risk factor in irinotecan (CPT-11) treatment of 5-FU-refractory colorectal cancer. Proc Am Soc Clin Oncol 16:260a [#921], 1997.

Pazdur R, Douillard J-Y, Skillings JR, et al. Multicenter phase III study of 5-fluorouracil (5-FU) or UFT™ in combination with leucovorin (LV) in patients with metastatic colorectal cancer. Proc Am Soc Clin Oncol 18:263a [#1009], 1999.

Bristol-Myers-Squibb Study 011; Transcript of 63rd Meeting of the Oncology Drug Advisory Committee, September 16th 1999.

Petrelli N, Douglass HO, Jr., Herrera L, et al. The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: a prospective randomized Phase III trial. J Clin Oncol 7:1419-1426, 1989.

Pommier Y, Tanizawa A, Kohn KW. Mechanisms of topoisomerase I inhibition by anticancer drugs. In: Liu LF, ed. Advances in Pharmacology. New York: Academic Press; 29B:73-92, 1994.

Poon MA, O'Connell MJ, Moertel CG, et al. Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. J Clin Oncol 7(10):1407-1418, 1989.

Rothenberg ML, Meropol NJ, Poplin EA et al. Deaths associated with irinotecan + bolus 5-fluorouracil/leucovorin: report of an independent panel, July 25, 2001.

Rothenberg ML, Meropol NJ, Poplin EA et al. Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. J Clin Oncol 19(9):3801-3807, 2001.

Rougier P, Milan C, Lazorthes F, et al. Prospective study of prognostic factors in patients with unresected hepatic metastases from colorectal cancer. Br J Surg 82:1397-400, 1995.

Sargent DJ, Goldberg RM, Mahoney MR, et al. Rapid reporting and review of an increased incidence of a known adverse event. J Natl Cancer Inst 92:1011-1013, 2000.

Sargent DJ, Goldberg RM, Jacobson SD, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. N Engl J Med 345(15):1091-1097, 2001.

Schaaf LJ, Ichhpurani AK, Elfring GL. Pharmacokinetics of CPT-11 and SN-38: a multicenter, open-label, phase II study of irinotecan hydrochloride (CPT-11) in patients with 5-fluorouracil (5-FU)-refractory colorectal cancer (M/6475/0006). Upjohn Technical Report 7215-95-035, October 24, 1995.

Schaaf L, Ichhpurani N, Elfring G, et al. Iinfluence of age on the pharmacokinetics of irinotecan (CPT-11) & its metabolites, SN-38 and SN-38 glucuronide (SN-38G), in patients with previously treated colorectal cancer. Proc Am Soc Clin Oncol 16:250a [#708], 1997.

Schaaf LJ, Rothenberg ML, Hammond LA et al. Phase I trial of weekly irinotecan (CPT-11) in patients with hepatic dysfunction. Proc Amer Soc Clin Oncol 20:220a [#402], 2001.

Shimada Y, Yoshino M, Wakui A, et al. Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. CPT-11 Gastrointestinal Cancer Study Group. J Clin Oncol 11(5):909-13, 1993.

Slatter JG, Sams JP, Hauer MJ, Vrbanac JJ, Schaaf LJ. Irinotecan hydrochloride (PNU-101440E, CPT-11): HPLC-radiometric quantitation of metabolites in urine, feces, and plasma following an intravenous dose of [^{14}C]PNU-101440E to patients with advanced solid tumor malignancy. Final report of the trial M/6475/0062. Pharmacia & Upjohn Study Report a0007369, 1998.

Schaaf LJ, Slatter JG, Sams JP, Feenstra KL, Johnson MG, Courtney M, Pearson LK, Cathcart KS, Verburg MT, Bothwell BE, Antal EJ. Irinotecan hydrochloride (CPT-11): phase I evaluation of the metabolism and excretion following intravenous administration of [^{14}C] irinotecan in patients with advanced solid tumor malignancy (Protocol M/6475/0062). Pharmacia & Upjohn Study Report a0010883, 1998.

Slatter JG, Schaaf LJ, Sams JP et al. Pharmacokinetics, metabolism, and excretion of irinotecan (CPT-11) following i.v. infusion of [^{14}C]CPT-11 in cancer patients. Drug Metab Disposition 28:423-33, 2000.

SU5416-031. A phase III randomized, open-label, multicenter, international study comparing the combination of SU5416/5-fluorouracil/leucovorin versus 5-fluorouracil/leucovorin alone as first-line therapy of patients with advanced colorectal cancer. Sugen, 2001 (ongoing study).

SU 5416-035. A phase III randomized, open-label, multicenter, international study comparing the combination of SU5416/irinotecan/5-fluorouracil/leucovorin versus irinotecan/5-fluorouracil/leucovorin alone as first-line therapy of patients with advanced colorectal cancer. Sugen, 2001 (ongoing study).

Tandem Corporation. Audit of oncology care patterns. October 2001.

V307. Multicentre, phase III open-label, randomized trial comparing CPT-11 in combination with a 5-FU/FA infusional regimen to the same 5-FU/FA infusional reigmen alone as adjuvant treatment for Stage II and III colon cancer. Aventis, 2001 (ongoing study).

Vanhoefer U, Harstrick A, Köhne CH, et al. Phase I study of a weekly schedule of irinotecan, high-dose leucovorin, and infusional fluorouracil as first-line chemotherapy in patients with advanced colorectal cancer. J Clin Oncol 17(3):907-13, 1999.

Venook A, Klein C, Kastrissios H, et al. Phase I study of irinotecan (CPT-11) in patients with abnormal liver or renal function or with prior pelvic radiation therapy. Proc Amer Soc Clin Oncol 20:70a [#293], 2001.

Von Hoff DD, Rothenberg ML, Pitot HC, et al. Irinotecan (CPT-11) therapy for patients with previously treated metastatic colorectal cancer (CRC): overall results of FDA-reviewed pivotal US clinical trials. Proc Am Soc Clin Oncol 16:228a [# 803], 1997.

Wasserman E, Myara A, Paumier D, et al. Baseline bilirubin and its transient early increase predicts likelihood of severe neutropenia and diarrhea in CPT-11-based chemotherapy. Proc Am Soc Clin Oncol 16:219a [# 767], 1997.

Wasserman E, Cuvier C, Lokiec F, et al. Combination of oxaliplatin plus irinotecan in patients with gastrointestinal tumors: results of two independent Phase I studies with pharmacokinetics. J Clin Oncol 17:1751-1759, 1999.

Weh HJ, Zschaber R, Cunningham D et al. A randomized phase III study comparing weekly folinic acid (FA) and high-dose 5-fluorouracil (5-FU) with monthly 5-FU/FA (day 1-5) in untreated patients with metastatic colorectal carcinoma. Onkologie 21:403-307, 1988.

Wolmark N, Rockette H, Mamounas E, et al. Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project C-04. J Clin Oncol 17:3553-3559, 1999.

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APPENDIX A – ADDITIONAL DATA – STUDIES 0038 AND V303

Table 1. Summary of Dose Modification Criteria – Studies 0038 and V303

Criterion	Study 0038	Study V303
Hematologic		
Grade 0 or 1	Maintain dose	Maintain dose
Grade 2	Reduce dose by 20%	Delay dose until grade ≤1, then give full dose
Grade 3	Omit dose until grade ≤1, then reduce by 20%	Delay dose until grade ≤1, then reduce by 20%
Grade 4	Omit dose until grade ≤1, then reduce by 40%	Delay dose until grade ≤1, then reduce by 20%
Neutropenic fever	Omit dose until grade ≤1, then reduce by 40%	Delay dose until grade ≤1, then reduce by 20%
Nonhematologic		
Grade 0 or 1	Maintain dose	Maintain dose
Grade 2	Reduce dose by 20%	Delay dose until grade ≤0, then give full dose
Grade 3	Omit dose, then reduce by 20%	Delay dose until grade ≤1, then reduce by 20%
Grade 4	Omit dose, then reduce by 40%	Delay dose until grade ≤1, then reduce by 20%

Table 2. Patient Enrollment Criteria – Studies 0038 and V303

Criterion	Study 0038	Study V303
General		
Measurable disease	Yes	Yes
Age	≥18 years of age	≥18–75 years of age
Performance status	0, 1, or 2	0, 1, or 2
Hematology		
WBC	≥3500/mm^3	--
ANC	≥1500/mm^3	ANC ≥2000
Hemoglobin	≥9 mg/dL	≥10 mg/dL
Platelets	≥100,000/mm^3	≥150,000/mm^3
Chemistry		
Bilirubin	≤2.0 mg/dL	≤1.25 x ULN (≤1.5 x ULN with hepatic metastases)
Transaminases	≤3 x ULN (or ≤5 x ULN with hepatic metastases)	≤3 x ULN (or ≤5 x ULN with hepatic metastases)
Creatinine	≤2.0 mg/dL	≤1.25 x ULN
Prior Therapy		
Adjuvant Therapy	Completed >12 months prior to study entry	Completed >6 months prior to study entry
Prior Radiotherapy	Not allowed	Allowed

Abbreviations: ANC = absolute neutrophil count, ULN = upper limit of normal, WBC = white blood count

Table 3. Patient Disposition by Study, Treatment Arm, and Patient Population – Studies 0038 and V303

Population	Study 0038			Study V303			
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV		5-FU/LV	
	Saltz Arm B	Mayo Clinic Arm C	Irinotecan Alone Arm A	Arm A		Arm B	
				AIO Arm A1	Douillard Arm A2	AIO Arm B1	deGramont Arm B2
As-randomized (n)	231*	226*	226	199		188	
				54	146	45	143
Untreated (n)	4	8	4	1		1	
				0	1	1	0
Full-analysis (n)	--	--	--	198*		187*	
				53	145	44	143
Treated with another arm (n)	2†‡	1§	1¶	0		1£	
				0	0	1	0
As-treated (n)	225¥	219¥	223¥	199¥		186¥	
				54¥	145¥	43¥	143¥

* Populations analyzed for efficacy
† Randomized to irinotecan/5-FU/LV but received 5-FU/LV
‡ Randomized to irinotecan/5-FU/LV but received irinotecan alone
§ Randomized to 5-FU/LV but received irinotecan alone
¶ Randomized to irinotecan alone but received 5-FU/LV
£ Randomized to 5-FU/LV but received irinotecan/5-FU/LV
¥ Populations analyzed for safety
Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin

Table 4. Baseline Patient Characteristics by Study, Treatment Arm, and Regimen – Studies 0038 and V303 (Intent-To-Treat Populations)

Adverse Event	Study 0038			Study V303			
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV		5-FU/LV	
	Saltz Arm B N = 231	Mayo Clinic Arm C N = 226	Irinotecan Alone Arm A N = 226	Arm A N = 198		Arm B N = 187	
				AIO Arm A1 N=53	Douillard Arm A2 N=145	AIO Arm B1 N=44	deGramont Arm B2 N=143
Median Age in years (range)	62 (25-85)	61 (19-85)	61 (30-87)	62 (27-75)		59 (24-75)	
				62 (31-75)	61 (27-74)	60 (24-75)	58 (31-75)
Gender (%)							
Male	65.4	54.4	64.2	66.7		52.9	
				54.7	71.0	52.3	53.2
Female	34.2	44.7	35.4	33.3		47.1	
				45.3	29.0	47.7	46.8
Performance Status (%)							
0	38.5	41.2	46.0	51.5		51.3	
				64.1	46.9	59.1	49.0
1	45.9	45.1	45.6	41.9		41.2	
				34.0	44.8	34.1	43.4
2	15.2	12.8	8.0	6.6		7.5	
				1.9	8.3	6.8	7.7
Prior Adjuvant Therapy (%)	10.8	8.0	10.2	25.8		23.5	
				24.5	26.2	22.7	23.8
Prior Radiotherapy (%)	3.0	2.2	1.3	20.2		15.5	
				18.9	20.7	11.4	16.8
Laboratory Abnormalities (%)							
LDH >ULN	60.0	55.7	53.3	43.0		44.9	
				48.0	40.7	35.7	48.3
SGOT >ULN	28.7	25.4	30.7	22.0		21.1	
				23.5	21.6	11.9	23.7
Total Bilirubin >ULN	6.6	4.1	10.0	6.6		7.0	
				3.9	7.6	4.6	7.8
WBC $\geq 8 \times 10^3/mm^3$	52.4	53.0	51.1	47.2		38.0	
				44.2	48.3	36.4	38.5
Hemoglobin <11 g/dL	25.6	25.3	25.8	16.2		21.4	
				13.2	17.2	18.2	22.4
Creatinine >ULN	7.1	3.7	5.4	5.1		6.0	
				9.6	3.5	11.4	4.3

* Data not available for some patients who were randomized but not treated.

Abbreviations: 5-FU = 5-fluorouracil, LDH = lactate dehydrogenase, LV = leucovorin, SGOT = serum glutamate-oxalate transferase, ULN = upper limit of normal, WBC = white blood count

Table 5. Baseline Patient Characteristics by Study, Treatment Arm, and Regimen – Studies 0038 and V303 (Treated Populations)

Adverse Event	Study 0038			Study V303			
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV		5-FU/LV	
	Saltz Arm B N = 225	Mayo Clinic Arm C N = 219	Irinotecan Alone Arm A N = 223	Arm A N = 199		Arm B N = 186	
				AIO Arm A1 N=54	Douillard Arm A2 N=145	AIO Arm B1 N=43	deGramont Arm B2 N=143
Median Age in years (range)	62 (25-85)	61 (19-85)	61 (30-87)	62 (27-75)		58.5 (24-75)	
				62 (31-75)	61 (27-74)	61 (24-75)	58 (31-75)
Gender (%)							
Male	65.3	55.3	64.1	66.3		53.2	
				53.7	71.0	53.5	53.2
Female	34.7	44.7	35.9	33.7		46.8	
				46.3	29.0	46.5	46.8
Performance Status (%)							
0	38.7	40.2	47.1	51.8		51.1	
				64.8	46.9	58.1	49.0
1	46.7	46.6	45.3	41.7		41.4	
				33.3	44.8	34.9	43.4
2	14.7	13.2	7.6	6.5		7.5	
				1.9	8.3	7.0	7.7
Prior Adjuvant Therapy (%)	11.1	8.2	9.9	25.6		23.7	
				24.1	26.2	23.3	23.8
Prior Radiotherapy (%)	2.7	2.3	1.4	20.1		15.6	
				18.5	20.7	11.6	16.8
Laboratory Abnormalities (%)							
LDH >ULN	60.3	55.5	53.3	42.8		45.2	
				47.1	40.7	36.6	48.3
SGOT >ULN	28.5	25.7	30.6	22.0		21.1	
				23.1	21.6	12.2	23.7
Total Bilirubin >ULN	6.7	4.1	10.0	6.6		7.0	
				3.8	7.6	4.7	7.8
WBC $\geq 8 \times 10^3/mm^3$	52.0	52.8	51.8	47.0		38.2	
				43.4	48.3	37.2	38.5
Hemoglobin <11 g/dL	25.8	25.2	25.7	16.1		21.5	
				13.0	17.2	18.6	22.4
Creatinine >ULN	7.1	3.7	5.4	5.1		6.0	
				9.4	3.5	11.6	4.3

Abbreviations: 5-FU = 5-fluorouracil, LDH = lactate dehydrogenase, LV = leucovorin, SGOT = serum glutamate-oxalate transferase, ULN = upper limit of normal, WBC = white blood count

Table 6. Efficacy Results by Study, Treatment Arm, and Regimen – Studies 0038 and V303
(Intent-to-Treat Populations)

Efficacy Endpoint	Study 0038			Study V303			
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV		5-FU/LV	
	Saltz Arm B N = 231	Mayo Clinic Arm C N = 226	Irinotecan Alone Arm A N = 226	Arm A N = 198		Arm B N = 187	
				AIO Arm A1 N=53	Douillard Arm A2 N=145	AIO Arm B1 N=44	deGramont Arm B2 N=143
Confirmed* Objective Tumor Response Rate, %	39.4	20.8	18.1	34.8		21.9	
				39.6	33.1	25.0	21.0
	(p<0.001)†			(p<0.005)†			
Median Duration of Objective Tumor Response, months	9.2	8.7	9.0	9.3		8.8	
				8.9	9.3	6.7	9.5
	(p=0.369)‡			(p=0.085)‡			
Median TTP, months	7.0	4.3	4.2	6.7		4.4	
				7.2	6.5	6.5	3.7
	(p=0.004)‡			(p<0.001)‡			
Median TTF, months	5.4	3.7	3.2	5.3		3.8	
				5.4	5.1	5.0	3.0
	(p=0.001)‡			(p=0.001)‡			
Median Survival, months	14.8	12.6	12.0	17.4		14.1	
				16.1	17.4	20.1	13.0
	(p=0.042)‡			(p=0.032)‡			

* Confirmed ≥4-6 weeks after first evidence of objective response
† Chi-square tests. In Study 0038, Arms B and C are compared. In Study V303, Arms A and B are compared.
‡ Unstratified log-rank tests. In Study 0038, Arms B and C are compared. In Study V303, Arms A and B are compared.
Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin, TTF = time to treatment failure, TTP = time to tumor progression

Table 7. Post-Study Therapy by Study and Treatment Arm – Studies 0038 and V303
(Patients with Follow-up Data)

Therapy	Study 0038				Study V303		
	Saltz Irinotecan 5-FU/LV	Mayo Clinic 5-FU/LV		Irinotecan	AIO/Douillard Irinotecan 5-FU/LV	AIO/de Gramont 5-FU/LV	
	Arm B N = 205 %	Arm C N = 203 %		Arm A N = 195 %	Arm A N = 167 %	Arm B N = 171 %	
Any Post-Study Therapy	52	70		79	49	65	
Irinotecan-based	1	38	56	3	2	28	34
Irinotecan/5-FU-based	13	18		9	4	6	
5-FU-based*	30	10		64	32	21	
Other therapy*	8	4		3	11	10	

* In Study 0038, includes patients receiving post-study oxaliplatin: Arm B – 5%; Arm C – 3%
In Study V303, includes patients receiving post-study oxaliplatin: Arm A – 19%; Arm B – 14%

Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin

Table 8. Adverse Events by Study, Treatment Arm, and Regimen – Studies 0038 and V303 (Treated Populations)

Adverse Event	Study 0038			Study V303			
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV		5-FU/LV	
	Saltz Arm B N = 225	Mayo Clinic Arm C N = 219	Irinotecan Alone Arm A N = 223	Arm A N = 199		Arm B N = 186	
				AIO Arm A1 N=54	Douillard Arm A2 N=145	AIO Arm B1 N=43	deGramont Arm B2 N=143
Diarrhea (%)							
Grade 3-4	22.7	13.2	31.0	22.6		10.8	
				44.5	14.4	25.6	6.3
Grade 3	15.1	5.9	18.4	35.2	10.3	14.0	4.2
Grade 4	7.6	7.3	12.6	9.3	4.1	11.6	2.1
Vomiting (%)							
Grade 3-4	9.7	4.1	12.1	5.5		3.2	
				11.2	3.5	4.7	2.8
Grade 3	5.3	2.7	5.8	9.3	2.8	0.0	1.4
Grade 4	4.4	1.4	6.3	1.9	0.7	4.7	1.4
Mucositis (%)							
Grade 3-4	2.2	16.9	2.2	3.0		2.7	
				0.0	4.1	2.3	2.8
Grade 3	1.8	14.6	2.2	0.0	4.1	2.3	2.8
Grade 4	0.4	2.3	0.0	0.0	0.0	0.0	0.0
Neutropenia (%)							
Grade 3-4	53.8	66.7	31.4	41.8		10.9	
				28.9	46.2	2.4	13.4
Grade 3	29.8	24.2	19.3	23.1	36.4	0.0	12.7
Grade 4	24.0	42.5	12.1	5.8	9.8	2.4	0.7
Grade 3-4 Neutropenia with Fever or Infection (%)							
Neutropenic fever/infection*	16.0	17.4	14.4	7.0		1.1	
				11.2	5.5	2.3	0.7
Hospitalization (%)							
Hospitalizations†	50.2	39.3	44.4	43.2		25.8	
				50.0	40.7	30.2	24.5
Discontinuation (%)							
Discontinuations due to adverse events‡	7.6	6.4	11.7	9.0		2.7	
				16.7	6.2	9.3	0.7

* Includes all events of neutropenic fever (concomitant grade 3-4 neutropenia and grade ≥2 fever) and neutropenic infection (concomitant grade 3-4 neutropenia and grade 3-4 infection or sepsis).

† Includes hospitalization for any reason (whether or not specifically related to toxic effects of study therapy).

‡ Includes discontinuations due to adverse events of any type and any potential cause (whether disease- or drug-related).

Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin

Table 9. Thromboembolic Events by Study, Treatment Arm, and Regimen – Studies 0038 and V303 (Treated Populations)

Adverse Event	Study 0038			Study V303			
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV		5-FU/LV	
	Saltz Arm B N = 225	Mayo Clinic Arm C N = 219	Irinotecan Alone Arm A N = 223	Arm A N = 199		Arm B N = 186	
				AIO Arm A1 N=54	Douillard Arm A2 N=145	AIO Arm B1 N=43	deGramont Arm B2 N=143
Any Event	9.3	11.4	5.4	12.1		5.4	
				13.0	11.7	4.7	5.6
All Venous Events*	7.1	8.2	4.0	8.0		3.2	
				9.3	7.6	0.0	4.2
Pulmonary Embolism†	2.7	1.4	0.9	0.0	1.4	0.0	0.7
All Arterial Events‡	2.7	3.2	1.3	4.0		2.2	
				3.7	4.1	4.7	1.4
Myocardial ischemia§	0.9	0.5	0.4	1.9	0.7	0.0	0.0
Myocardial infarction¶	1.3	0.0	0.4	0.0	0.0	4.7	0.0
Cardiac arrest/sudden death£	0.0	2.3	0.0	0.0	0.0	0.0	0.7
Cerebral ischemia/infarction¥	0.0	0.0	0.4	0.0	1.4	0.0	0.7
Peripheral arterial#	0.4	0.5	0.0	1.9	2.1	0.0	0.0

* Based on review of COSTART terms: deep thrombophlebitis, pulmonary embolus, thrombophlebitis, thrombosis, vascular disorder
Includes patients: 0038: Arm B – 033, 054@, 072, 074, 129, 138@, 150, 205@, 239, 374, 447, 480@, 578, 603@, 658, 692
0038: Arm C – 010, 015@, 040@, 044, 094@, 113, 126@, 163, 177, 178, 182, 224@, 478, 563, 566, 569, 657, 678@
0038: Arm A – 108, 145@, 160, 204@, 312, 495@, 612@, 679@, 686
V303: Arm A1 – 01506, 07204@, 07207@, 08202@, 16201@
V303: Arm A2 – 01204@, 04307@, 05104, 05601@, 05612@, 06404, 12102@, 19201@, 19303, 22106@, 22305@
V303: Arm B2 – 04210@, 04305@, 19802, 19806@, 19910, 23009@

† Includes patients: 0038: Arm B – 054, 072, 129, 205, 374, 603
0038: Arm C – 015, 126, 569
0038: Arm A – 108, 204
V303: Arm A2 – 19303, 22305 (from narrative: pleuritic chest pain, dyspnea→death)
V303: Arm B2 – 04305

‡ Based on review of COSTART terms: angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, embolus lower extremity, heart arrest, myocardial infarct, myocardial ischemia, peripheral vascular disorder, sudden death
Includes patients: 0038: Arm B – 128, 279, 348, 317, 374, 562@
0038: Arm C – 005, 093@, 283@, 337, 373@, 383@, 456@
0038: Arm A – 234@, 308, 459
V303: Arm A1 – 02506, 16202@
V303: Arm A2 – 04310, 05202@, 05617, 06901@, 19805, 22208@
V303: Arm B1 – 08301@, 11207@
V303: Arm B2 – 06402@, 22108

§ Includes patients: 0038: Arm B – 279, 348
0038: Arm C – 383
0038: Arm A – 308
V303: Arm A1 – 16202
V303: Arm A2 – 06901

¶ Includes patients: 0038: Arm B – 317, 374, 562
0038: Arm A – 234
V303: Arm B1 – 08301, 11207

£ Includes patients: 0038: Arm C – 005, 093, 283, 373, 456
V303: Arm B2 – 22108

¥ Includes patients: 0038: Arm A – 459
V303: Arm A2 – 22208, 05617 (from narrative: sudden coma→death)
V303: Arm B2 – 06402

\# Includes patients: 0038: Arm B – 128
0038: Arm C – 337 (peripheral vascular disease)
V303: Arm A1 – 02506
V303: Arm A2 – 04310, 05202, 19805

@ First-cycle event.

Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin

Table 10. Overview of Deaths by Study, Treatment Arm, and Regimen – Studies 0038 and V303 (Treated Populations)

Categorization	Study 0038			Study V303			
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV		5-FU/LV	
	Saltz Arm B N = 225	Mayo Clinic Arm C N = 219	Irinotecan Alone Arm A N = 223	Arm A N = 199		Arm B N = 186	
				AIO Arm A1 N=54	Douillard Arm A2 N=145	AIO Arm B1 N=43	deGramont Arm B2 N=143
All Causes Throughout Entire Follow-Up Period	73.3	83.1	79.4	63.8		72.6	
				61.1	64.8	55.8	77.6
All Causes With 60 Days From Start Of Therapy	6.7	7.3	6.7	2.0		2.2	
				1.9	2.1	4.7	1.4
All Causes During or Within 30 Days from Last Therapy	9.3	6.8	5.8	4.0		3.3	
				3.8	4.2	4.6	2.8
Cytotoxic or Vascular Events Present (Monitor Assessment)	3.1	5.0	2.7	2.5		2.2	
				1.9	2.8	2.3	2.1
Cytotoxic Events Present (Monitor Assessment	*3.1**	*2.3*†	*2.2*‡	*1.0*		*0.0*	
				0.0	*1.4*¥	*0.0*	*0.0*
Vascular Events Present or Sudden Death (Monitor Assessment)	*0.4*§	*2.7*¶	*0.5*£	*2.0*		*2.2*	
				1.9#	*2.1*@	*2.3*&	*2.1*ψ
Progressive Disease or Other Event Present∞ (Monitor Assessment)	6.2	1.8	3.1	1.5		1.1	
				1.9	1.4	2.3	0.7
All Causes During or Within 30 Days from Last Therapy in First Cycle	5.3	4.1	3.6	2.0		2.2	
				1.9	2.1	4.7	1.4
Drug-related (Investigator Assessment)	0.9	1.4	0.9	0.5		0.0	
				0.0	0.7	0.0	0.0

* Includes patients: Cycle 1 – 041, 329, 428, 547, 610, 562 (patient also had vascular event); Cycle ≥2 – 534
† Includes patients: Cycle 1 – 025, 093, 193; Cycle ≥2 – 465, 687
‡ Includes patients: Cycle 1 – 134, 564; Cycle ≥2 – 211, 371, 413
§ Includes patients: Cycle 1 – 562 (patient also had cytotoxic event)
¶ Includes patients: Cycle 1 – 015, 126, 283, 373, 456; ≥Cycle 2 – 005
£ Includes patients: Cycle ≥2 – 108
¥ Includes patients: Cycle 1 – 01204 (patient also had vascular event), 22204
\# Includes patients: Cycle 1 – 01502
@ Includes patients: Cycle 1 – 01204 (patient also had cytotoxic event), 22305; Cycle ≥2 – 05617
& Includes patients: Cycle 1 – 08301
ψ Includes patients: Cycle 1 – 04305, 06402; Cycle ≥2 – 22108
∞ All remaining patients had progressive disease except patients 023 (lactic acidosis) and 243 (nonneutropenic pneumonitis) in ≥Cycle 2 of Arm B, Study 0038
Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin

Table 11. Supportive Care by Study, Treatment Arm, and Regimen – Studies 0038 and V303 (Treated Populations)

Adverse Event	Study 0038			Study V303			
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV		5-FU/LV	
	Saltz Arm B N = 225	Mayo Clinic Arm C N = 219	Irinotecan Alone Arm A N = 223	Arm A N = 199		Arm B N = 186	
				AIO Arm A1 N=54	Douillard Arm A2 N=145	AIO Arm B1 N=43	deGramont Arm B2 N=143
Antiemetics (%)							
Dexamethasone	92.9	19.6	88.3	61.1	44.8	20.9	18.9
Serotonin Antagonists*	64.4	12.8	59.6	85.2	86.9	32.6	34.3
Phenothiazines†	53.3	53.9	54.7	7.4	12.4	9.3	8.4
Dopamine Antagonists‡	31.6	23.7	21.1	37.0	61.4	53.5	53.2
Anticholinergics (%)							
Atropine and Others§	19.1	3.2	23.3	33.3	33.8	11.6	2.1
Mouth Care (%)							
Stomatologicals¶	21.8	51.1	12.1	13.0	11.6	31.7	28.0
Antidiarrheals (%)							
Loperamide	76.4	53.4	78.5	75.9	59.3	44.2	21.0
Others£	17.8	9.6	19.7	1.9	4.8	4.7	1.4
Octreotide	5.8	2.7	6.7	7.4	1.4	2.3	0.7
Antibiotics (%)							
Fluoroquinolones¥	20.0	21.0	18.4	42.6	27.6	16.3	14.7
Colony-Stimulating Factors (%)							
G-CSF/GM-CSF	8.0	5.9	6.7	1.9	2.1	0	1.4

* Includes granisetron, ondansetron, dolasetron, and similar agents
† Includes primarily prochlorperazine, but also chlorpromazine, promethazine, thiethylperazine, and similar agents
‡ Includes primarily metoclopramide
§ Includes hyoscyamine, scopolamine, and similar agents
¶ Includes various oral mixtures of topical anesthetics, antacids, antibiotics, glycerin, sucralfate, and similar agents
£ Includes other antipropulsives (eg, diphenoxylate with atropine [Lomotil®])
¥ Includes fluoroquinolones given for any reason.
Abbreviations: 5-FU = 5-fluorouracil, G-CSF = granulocyte colony-stimulating factor, GM-CSF = granulocyte-macrophage colony-stimulating factor, LV = leucovorin

Commentary: In Study 0038, differences between treatment arms in percentages of patients receiving concomitant antiemetics, anticholinergics, mouth care, and antidiarrheals were generally consistent with the relative frequencies of the supported adverse events for the treatment regimens. Patients in treatment groups receiving irinotecan (either Saltz irinotecan/5-FU/LV or irinotecan alone) received antiemetics, anticholinergics, or antidiarrheals more frequently than did patients treated with Mayo Clinic 5-FU/LV alone. Patients treated with irinotecan-based therapy were more likely to be supported with dexamethasone and serotonin antagonists (eg, ondansetron or granisetron) for antiemetic prophylaxis. Conversely, the need for mouth care because of mucositis was greater with Mayo Clinic 5-FU/LV than with irinotecan-based treatment. Of interest, although it was not mandated by protocol, approximately 20% of the patients across the arms received fluoroquinolone antibiotic therapy. The most common explanation given for such use was neutropenic fever prophylaxis (not prophylaxis of infection in conjunction with diarrhea) and may explain the lack of increase in use with combination Saltz irinotecan/5-FU/LV therapy relative to Mayo Clinic 5-FU/LV (since use of Saltz irinotecan/5-FU/LV did not increase neutropenia or neutropenic fever risk relative to Mayo Clinic 5-FU/LV). G-CSF support was infrequent and was provided to comparable percentages of patients across the treatment arms.

As in Study 0038, the differences between the Study V303 treatment arms in percentages of patients receiving concomitant antiemetics, anticholinergics, and antidiarrheals were consistent with the relative frequencies of the supported adverse events for the treatment regimens. Patients treated with irinotecan/5-FU/LV received all of these types of drugs more frequently than did patients treated with 5-FU/LV alone. Patients treated with irinotecan-based therapy were more likely to be supported with dexamethasone and serotonin antagonists (eg, ondansetron or granisetron). The difference in rates of dexamethasone use with irinotecan/5-FU/LV in Study V303 relative to Study 0038 are likely engendered by a protocol recommendation in Study 0038 that dexamethasone be included as part of the antiemetic regimen. Conversely, it is notable that patients in Study V303 were more likely to receive highly effective and specific antiemetics (eg, serotonin or dopamine antagonists) than patients in Study 0038. The lack of phenothiazine use in Study V303 probably reflect regional differences in commonly used antiemetics. In Study V303, fluoroquinolone use was greater among patients given irinotecan/5-FU/LV. Colony-stimulating factor support was infrequent in Study V303, as it was in Study 0038.

Table 12. Early Adverse Outcomes by Performance Status for the Mayo Clinic and de Gramont 5-FU/LV Regimens – Studies 0038 and V303

Baseline Characteristic	First-Cycle Events												Death ≤60 days from First Therapy
	n	Grade 3-4 Diarrhea	Grade 3-4 Vomiting	Thrombo-embolism	Neutropenia		Neutro-penia with Fever or Infection†	Hospita-lizations‡	Disconti-nuations due to Adverse Events§	Deaths ≤30 days from Last Therapy¶	Combined Adverse Outcomes£	Failed to Complete Cycle 1¥	
					Grade 3-4	Grade 4							
Study 0038 (%)													
0	88	5.7	3.4	**1.1****	47.7	20.5	11.4	**8.0***	3.4	**1.1***	**18.2***	8.0	**2.3*****
1	102	6.9	2.0	**4.9**	50.0	29.4	14.7	**20.6**	2.0	**3.9**	**28.4**	12.8	**6.9**
2	29	0.0	0.0	**17.2**	37.9	27.6	17.2	**31.0**	0.0	**13.8**	**44.8**	17.2	**24.1**
All Patients (%)	219	5.5	2.3	5.0	47.5	25.6	13.7	16.9	2.3	4.1	26.5	11.4	7.3
Study V303 (%)													
0	70	2.9	0.0	4.3	5.7	0.0	0.0	14.3	0.0	0.0	14.3	20.0	0.0
1	62	6.5	3.2	3.2	1.6	0.0	1.6	11.3	0.0	3.2	11.3	16.1	3.2
2	11	9.1	9.1	0.0	0.0	0.0	0.0	36.4	0.0	0.0	36.5	45.5	0.0
All Patients (%)	143	4.9	2.1	3.5	3.5	0.0	0.7	14.7	0.0	1.4	14.7	20.3	1.4

Statistical significance was assessed by logistic regression analysis with forward selection ($p<0.1$ for entry) and age as a continuous variable. All baseline variables (including laboratory variables) were considered with the following exceptions: Study 0038 – prior radiation (which had too few patients to categorize); Study V303 -- baseline serum LDH in (which was not routinely collected in all patients) and baseline serum creatinine (which had too few patients to categorize). Significant differences are noted in red. Where applicable, severity was graded by NCI CTC, Version 1.0.

† Includes patients with simultaneous occurrence of grade 3-4 neutropenia or leucopenia with grade ≥2 fever or grade 3-4 bacterial or fungal infections or sepsis.

‡ Includes patients hospitalized for any cause (whether or not specifically related to toxic effects of study therapy). Patients hospitalized more than once are counted only once in this analysis.

§ Includes discontinuations due to adverse events of any type.

¶ Includes patients who only received first-cycle therapy and died within 30 days of the last administration of study treatment.

£ Includes patients with simultaneous occurrence of grade 3-4 neutropenia or leucopenia with grade ≥2 fever or grade 3-4 bacterial or fungal infections or sepsis; hospitalization for any cause (whether or not specifically related to toxic effects of study therapy); discontinuations due to adverse events of any type; and/or patients who only received first-cycle therapy and died within 30 days of the last administration of study treatment.

¥ Includes patients who did not enter Cycle 2.

* $p\leq0.05$, ** $p\leq0.01$, *** $p\leq0.001$

Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin, ND = not done

APPENDIX B – INDEPENDENT REVIEW PANEL REPORT

Rothenberg ML, Meropol NJ, Poplin EA et al. Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. J Clin Oncol 19:3801-3807, 2001.

SPECIAL ARTICLE

Mortality Associated With Irinotecan Plus Bolus Fluorouracil/Leucovorin: Summary Findings of an Independent Panel

By Mace L. Rothenberg, Neal J. Meropol, Elizabeth A. Poplin, Eric Van Cutsem, and Scott Wadler

Purpose: **To review and assign attribution for the causes of early deaths on two National Cancer Institute-sponsored cooperative group studies involving irinotecan and bolus fluorouracil (5-FU) and leucovorin (IFL).**

Patients and Methods: **The inpatient, outpatient, and research records of patients treated on Cancer and Leukemia Group B protocol C89803 and on North Center Cancer Treatment Group protocol N9741 were reviewed by a panel of five medical oncologists not directly involved with either study. Each death was categorized as treatment-induced, treatment-exacerbated, or treatment-unrelated.**

Results: **The records of 44 patients who experienced early deaths on C89803 (21 patients) or N9741 (23 patients) were reviewed. Patients treated with irinotecan plus bolus 5-FU/leucovorin had a three-fold higher rate of treatment-induced or treatment-exacerbated death than patients treated on the other arm(s) of the respective studies. For C89803, these rates were 2.5% (16 of 635) for IFL versus 0.8% (five of 628) for bolus weekly 5-FU and leucovorin. For N9741, these rates were 3.5% (10 of 289) for IFL, 1.1% (three of 277) for oxaliplatin plus bolus and infusional 5-FU and leucovorin, and 1.1% (three of 275) for oxaliplatin plus irinotecan. Multiple gastrointestinal toxicities that often occurred together were characterized into a gastrointestinal syndrome. Sudden, unexpected thromboembolic events were characterized as a vascular syndrome. The majority of deaths in both studies were attributable to one or both of these syndromes.**

Conclusion: **Close clinical monitoring, early recognition of toxicities and toxicity syndromes, aggressive therapeutic intervention, and withholding therapy in the presence of unresolved drug-related toxicities is recommended for patients receiving IFL or other intensive chemotherapy regimens.**

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IN 1999, THE RESULTS of two large, randomized studies were reported that indicated that the addition of irinotecan (CPT-11; Camptosar, Pharmacia Corp, Peapack, NJ) to fluorouracil (5-FU) and leucovorin improved survival in patients with advanced-stage colorectal cancer.[1,2] These data led to the supplemental approval of irinotecan in March 2000 for use in first-line therapy for patients with metastatic colorectal cancer. It is estimated that 60% to 70% of patients with metastatic colorectal cancer receive irinotecan, fluorouracil, and leucovorin (IFL) as first-line chemotherapy in the United States.

In October 1998, the North Central Cancer Treatment Group (NCCTG) opened N9741, a phase III intergroup trial that compared several investigational combination chemotherapy regimens with 5-FU and leucovorin (daily × 5 days, Mayo Clinic schedule) in patients with metastatic colorectal cancer. The study was amended in March 2000 to terminate two experimental arms that were associated with unexpectedly high death rates and also to terminate the 5-FU plus leucovorin control arm.[3] The trial was revised into a three-arm study with IFL, administered in the fashion described by Saltz et al,[1] which became the new control arm. By the Spring of 2001, 841 of a planned 1,125 patients had been enrolled onto the three remaining arms of N9741: 289 treated with IFL, 277 treated with oxaliplatin plus bolus and infusional 5-FU plus leucovorin,[4] and 275 treated with oxaliplatin plus irinotecan on a once-every-3-weeks regimen.[5]

In April 1999, the Cancer and Leukemia Group B (CALGB) opened C89803, a phase III intergroup trial that compared IFL, administered as described by Saltz et al,[1] against 5-FU and leucovorin (weekly × 6 weeks, followed by a 2-week rest, Roswell Park schedule)[6] as adjuvant therapy in patients with Dukes' stage C (tumor-node-metastasis system stage III) colon cancer. By the Spring of 2001, the initial accrual goal of this study had been reached.

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This review was conducted by an independent panel and neither of these parties was involved in the generation of this report.

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A total of 1,263 patients were enrolled onto C89803: 635 treated with IFL and 628 treated with 5-FU and leucovorin by the Roswell Park weekly schedule.

On April 24, 2001, the NCCTG External Data Monitoring Committee identified an unexpected number of deaths that occurred within the first 60 days of study entry onto protocol N9741. In addition, it seemed that there were a disproportionate number of deaths that occurred in patients treated on the IFL control arm of the study. There were 14 deaths (4.8%) in 289 patients treated on the IFL arm; five deaths (1.8%) in 277 patients treated with the oxaliplatin, 5-FU, and leucovorin regimen; and five deaths (1.8%) in 275 patients treated with the oxaliplatin plus irinotecan regimen.[3,7] To place these results in proper context, the treatment-related death rate in the original study that evaluated irinotecan plus bolus 5-FU and leucovorin was reported as 0.9% (two deaths in 225 patients)[1] and the toxic death rates in other recent phase III trials were similar to this, ranging from 0.2% to 1.3%.[8,9]

These findings prompted a CALGB internal review of the early death rate in C89803. This review identified 19 deaths within the first 60 days of treatment: 14 (2.2%) of 635 patients treated with IFL and five (0.8%) of 628 patients treated with 5-FU and leucovorin.[7] To place these results in context, the death rate for patients treated on other recently reported colon cancer adjuvant studies ranged from 0% to 0.8%.[10,11]

After a series of conference calls in April 2001, the NCCTG suspended accrual onto N9741 on April 25, 2001, and the CALGB permanently closed accrual to C89803 on April 27, 2001. In addition to halting accrual, representatives of CALGB, NCCTG, Pharmacia, and the Cancer Therapy Evaluation Program of the National Cancer Institute (NCI) agreed that an independent review panel should be convened to review the medical records of the patients who experienced early death on both studies. This article summarizes the findings of that review panel.

The charge to the committee was to assign attribution for each death; to review the management of each patient with respect to protocol eligibility, chemotherapy administration, and adherence to dose-modification guidelines; and to identify a risk profile that might allow prospective identification of patients at high risk for early death.

PATIENTS AND METHODS

Data Retrieval

Between June and July, 2001, Theradex staff members visited each site at which an early death of a patient occurred on either N9741 or C89803. The records of one patient who died within 60 days of randomization were not reviewed because the patient was removed from study before the initiation of protocol treatment. At the request of the cooperative groups, one patient who died on day 62 of protocol treatment on N9741 and one patient who died on day 82 of protocol treatment on C89803 were included in this analysis because of concerns that these deaths were treatment-related. Therefore, this review was conducted from the records of 23 patients from N9741 and 21 patients from C89803.

Copies were made of all inpatient and outpatient treatment records as well as research records. All patient identifiers were deleted from the copies of the records made available to the reviewers. All patients were identified only by the unique numbers assigned by the respective cooperative group.

Data Abstraction

Theradex staff members abstracted critical data on each patient to assist in this review. This abstraction consisted of an eligibility summary, a summary of results of prestudy evaluations, a listing of prestudy and concomitant medication administered to each patient and categorized by known interactions with cytochrome p450 isozyme 3A4, and a chronologic summary of the clinical course that included drug dosages, dates of administration, adverse events, and medical interventions from the time of treatment initiation to the time of patient death.

Panel Review

This review was conducted in Princeton, NJ from July 13-15, 2001, by a panel of five medical oncologists not directly involved in either of the two studies. Copies of the entire inpatient and outpatient medical records of each patient were reviewed. Where available, autopsy reports were included in the patient record. Each patient record was independently reviewed in detail by one primary and one or two secondary reviewers. Each case was then discussed by the group to reach a consensus on the cause of death.

Criteria for Attribution of Cause of Death

In preparation for this review, the panel inquired about guidelines for attribution of death of a patient while on a clinical trial. The panel was informed that no such guidelines existed within the two involved cooperative groups, the Cancer Therapy Evaluation Program of the NCI, the Food and Drug Administration, or the Office for Human Research Protections of the Department of Health and Human Services. The existing system describes deaths on study as being treatment-related or treatment-unrelated, with qualifiers of none, unlikely, possible, probably, or definite used to convey the degree of certainty for the cause of death. The panel felt that this approach yielded so many different categories as to not be clinically useful. It was recognized that this system was most deficient in determining the cause of death in situations in which multiple adverse events occurred simultaneously. The inability of this system to identify the relative contributions of the therapy, the disease, and any underlying medical conditions to the patient's demise prompted the panel to consider an alternative method for death attribution.

The panel developed and used the following categories in an attempt to provide a more useful and clearer perspective on the cause of deaths on study. These definitions were developed in advance of the meeting and applied prospectively in the review of these records.

- Treatment-induced: Death clearly caused by protocol treatment.
- Treatment-unrelated: Death clearly unrelated to protocol treatment.

Table 1. Causes of Early Deaths on C89803

Treatment Arm	Total Deaths		Treatment-Induced Deaths		Treatment-Exacerbated Deaths		Treatment-Unrelated Deaths (no.)
	No.	%	No.	%	No.	%	
Irinotecan + bolus 5-FU/leucovorin	16/635	2.5*	15/635	2.4	1/635	0.2	0
Roswell Park 5-FU/leucovorin	5/628	0.8	5/628	0.8	0		0
Total	21		20		1		0

NOTE. No. of patients/total no. patients treated with therapy.
*Includes one patient who died on day 82 of the study.

- Treatment-exacerbated: Death caused by exacerbation of an underlying medical disorder by protocol treatment. The medical disorder had to be pre-existing at the time of initiation of treatment. The patient's death would not have been expected in that time frame from the underlying condition had protocol treatment not been administered.

Limitations of Review

With three exceptions, as noted above, this review was limited to those patients who died within 60 days of initiation of protocol treatment. Because this analysis did not include patients who experienced severe but nonlethal toxicities or those who developed moderate, mild, or no toxicities, we could not create a risk profile for those patients most likely to encounter varying degrees of toxicity or die while receiving treatment. Our conclusions are, therefore, descriptive and rely solely on the observations made from the subset of patients who experienced early deaths on study.

RESULTS

Deaths in Each Treatment Arm and Attribution

CALGB 89803. Twenty patients died within 60 days of initiation of treatment. One additional patient who died on day 82 was added to this analysis at the request of the cooperative group. The causes of death, using the categories defined above, are listed in Table 1.

N9741. Twenty-three patients died within 60 days of study registration. One patient who was registered but never treated is not included in this analysis. One patient who died on day 62 was added to this analysis at the request of the cooperative group. The causes of death, using the categories defined above, are listed in Table 2.

There were triple the number of treatment-induced and treatment-exacerbated deaths on the IFL arms of each study compared with the other arms. Treatment-induced deaths were rarely because of any single toxicity. Deaths were most commonly the result of a cluster of toxicities that occurred simultaneously or in rapid succession. Summary tables that list the frequency and severity of individual toxicities but provide no information on the simultaneous occurrence of multiple toxicities do not adequately capture the full clinical impact of these episodes. Often, it was the combined effect of several moderate or severe toxicities that directly led to the patient's death.

Certain toxicities often occurred in association with other toxicities, especially in those patients treated with irinotecan plus bolus 5-FU and leucovorin. These concurrent or overlapping toxicities could be characterized into two syndromes.

Gastrointestinal Syndrome

This was defined as a constellation of gastrointestinal symptoms, including diarrhea, nausea, vomiting, anorexia, and abdominal cramping. Symptoms were often associated with severe dehydration, neutropenia, fever, and electrolyte abnormalities. Radiographic findings associated with this

Table 2. Causes of Early Deaths on N9741

Treatment Arm	Total Deaths		Treatment-Induced Deaths		Treatment-Exacerbated Deaths		Treatment-Unrelated Deaths	
	No.	%	No.	%	No.	%	No.	%
Irinotecan + bolus 5-FU/leucovorin	13/289	4.5	9/289	3.1	1/289	0.3	3/289	1.0
Oxaliplatin + bolus and infusional 5-FU/leucovorin	5/277	1.8*	2/277	0.7	1/277	0.4	2/277	0.7
Oxaliplatin + irinotecan	5/275	1.8	3/275	1.1	0		2/275	0.7
Total	23		14		2		7	

NOTE. No. of patients/total no. of patients treated with therapy.
*Includes one patient who died on day 62 of treatment and excludes one patient who was registered but never treated on study.

Table 3. Gastrointestinal and/or Vascular Syndromes as the Cause of Deaths on C89803

Treatment Arm	Treatment-Induced or Exacerbated Deaths		Gastrointestinal Syndrome–Induced or Exacerbated Deaths		Vascular Syndrome–Induced or Exacerbated Deaths		Deaths Due to Neither Syndrome	
	No.	%	No.	%	No.	%	No.	%
Irinotecan + bolus 5-FU/leucovorin	16/635	2.5	12*/635	1.9	5*†/635	0.8	2/635	0.3
Roswell Park 5-FU/leucovorin	5/628	0.8	4/628	0.6	1‡/628	0.2	0	
Total	21		16		6		2	

NOTE. No. of patients/total no. of patients treated with therapy.

*Three patients experienced both syndromes and are therefore included in both columns.

†These vascular episodes were comprised of two myocardial infarctions, one pulmonary embolus, one cerebrovascular accident, and one pulmonary embolus or myocardial infarction.

‡This vascular episode was comprised of a myocardial infarction.

syndrome often included dilated bowel, air-fluid levels without anatomic obstruction, and thickened bowel wall.

Vascular Syndrome

This was defined as an acute, fatal myocardial infarction, pulmonary embolus, or cerebrovascular accident that occurred during or shortly after receiving chemotherapy. An underlying cardiovascular or thromboembolic condition may have been present, but if so it was stable or well-compensated at the time of initiation of treatment. The vascular event was not attributable solely to other treatment-induced toxicities (eg, severe dehydration) or other known causes (eg, immobility for a patient who develops a pulmonary embolus). The vascular syndrome may have occurred as an isolated event or in association with gastrointestinal or other drug-induced toxicities.

When these definitions were applied to the treatment-induced or treatment-exacerbated deaths described in Tables 1 and 2, they were frequently found to be associated with early mortality. These results are listed in Tables 3 and 4.

Time to Fatal Events

C89803. For those patients included in this analysis, the rapidity with which death occurred seemed to differ on the basis of treatment. For patients treated with the Roswell Park 5-FU and leucovorin regimen, the median time of death was day 47. For those patients treated with IFL, the median time of death was day 29. All 21 patients are included in this analysis because all deaths were either treatment-induced or treatment-exacerbated. Patients who died on the IFL arm of C89803 often had moderate to severe toxicities that resulted in dose attenuation but not treatment suspension prior to death. In contrast, patients who died on the Roswell Park arm of the study had few preceding toxicities and were treated on time and at full doses prior to the onset of fatal toxicities, which suggests a more acute onset of severe toxicity with weekly bolus 5-FU plus leucovorin than with IFL.

N9741. Differences in the interval between initiation of treatment and death are more difficult to assess on N9741 because some patients clearly died from cancer progression.

Table 4. Gastrointestinal and/or Vascular Syndromes as the Cause of Deaths on N9741

NCCTG 9741	Treatment-Induced or Exacerbated Deaths		Gastrointestinal Syndrome–Induced or Exacerbated Deaths		Vascular Syndrome–Induced or Exacerbated Deaths		Deaths Due to Neither Syndrome	
	No.	%	No.	%	No.	%	No.	%
Irinotecan + bolus 5-FU/leucovorin	10/289	3.5	6*/289	2.1	3*†/289	1.0	3/289	1.0
Oxaliplatin + bolus and infusional 5-FU/leucovorin	3/277	1.1	0		1/277	0.4	2/277	0.7
Oxaliplatin + irinotecan	3/275	1.1	1/275	0.4	0		2/275	0.7
Total	16		7		4		7	

NOTE. No. of patients/total no. of patients treated with therapy.

*Two patients experienced both syndromes and are, therefore, included in both columns.

†These vascular episodes were comprised of one myocardial infarction, one pulmonary embolus, and one cerebrovascular accident.

The median days of death for patients treated on each arm of N9741 were as follows: IFL, day 30; oxaliplatin + bolus and infusional 5-FU/leucovorin, day 30; and oxaliplatin + irinotecan, day 18. When this analysis was limited to the 16 patients who experienced treatment-related or treatment-exacerbated deaths, the median days of death were 28, 26, and 18, respectively. Although there does not seem to be any marked difference in the time to treatment-related death between groups when such patients are included or excluded from the analysis, it was noted that the median time to death in all three regimens was 30 days or less from the time of initiation of treatment.

Baseline Characteristics of Patients Who Died

The median age of patients who died in the control group of C89803 was 73 years, and the median age of patients who died in the IFL-treated group in C89803 was 69.5 years. These median ages are somewhat higher than the typical median ages of 60 to 63 years in patients enrolled onto cooperative group adjuvant colon cancer studies.[10,11]

The median ages of patients who died on each of the arms of N9741 were as follows: IFL group, 65 years; oxaliplatin + bolus and infusional 5-FU/leucovorin, 66 years; and oxaliplatin + irinotecan group, 68 years. However, when deaths that were considered to be treatment-unrelated are removed from this analysis, the ages tend to go up in all three groups. The median age of patients who died from treatment-induced or treatment-exacerbated causes on each of the arms of N9741 now became the following: IFL group, 69 years; oxaliplatin + bolus and infusional 5-FU/leucovorin, 66 years; and oxaliplatin + irinotecan, 69 years. These median ages also seemed to be somewhat higher, especially in the two irinotecan-containing arms, than the median ages of 61 and 62 years for patients enrolled onto the two prior phase III studies of IFL in patients with advanced-stage colorectal cancer.[1,2] Conclusions that can be drawn from these analyses are limited due to the unavailability of data on the ages of all patients treated on C89803 and N9741.

Location of the primary tumor (right-sided *v* left-sided) was also examined in this analysis. There did not seem to be a substantial difference in the representation of right-sided or left-sided primary tumors in patients who experienced early death on study.

Early deaths were observed in patients from all baseline performance status levels, Eastern Cooperative Oncology Group 0, 1, and 2. Although there did not seem to be a quantitative difference in the number of patients with any particular PS who experienced early death on study, it was recognized that the majority of patients enrolled onto these studies entered with PS of 0 or 1. An analysis of death rate by PS would be of interest to determine whether one group was at disproportionate risk for early death from any of these treatments. Concomitant medications, including known cytochrome p450 isozyme 3A4 substrates, inhibitors, and inducers did not have an obvious relationship with fatal events.

Patient Eligibility

Virtually all patients included in this review met eligibility criteria as outlined in the respective studies. The eligibility of one patient was questioned because of the lack of pathologic tissue from the presumed cecal primary, a pattern of serum tumor markers that suggested a primary tumor other than colon cancer (CA-125 was elevated out of proportion to carcinoembryonic antigen), and borderline performance status at the time of enrollment.

Treatment Administration and Adherence to Dose Modification Guideline

Isolated cases of dosing errors were noted, but no systematic problems were identified regarding adherence to protocol treatment or dose modification.

RECOMMENDATIONS

General

1. Improved criteria should be developed for attribution of cause of death that occurs in any patient who receives protocol treatment. One approach is proposed in which death is categorized as treatment-induced, treatment-unrelated, or treatment-exacerbated. This was the first time that these criteria were used, and they are open to critique and revision.

2. Real-time monitoring of life-threatening or fatal adverse events or hospitalizations can hasten identification of unexpectedly frequent or severe clinical toxicities in a multicenter trial and could enhance patient safety on clinical trials.[13]

Specific

1. Increased awareness is needed among health care providers regarding the described gastrointestinal and vascular syndromes associated with irinotecan plus bolus 5-FU and leucovorin treatment.

2. Patients treated with IFL should undergo weekly assessment, at least during the first cycle of treatment, by a clinician who is experienced in the use of this regimen and in the treatment of gastrointestinal cancer. This is especially important prior to weeks 3 and 4 of treatment, when most of the severe treatment-related toxicities that led to early death occurred. In general, more stringent guidelines are needed for

monitoring patients who are receiving IFL or any of the newer, more intensive combination chemotherapy regimens.

3. A more aggressive approach should be taken in the treatment of diarrhea that occurs in isolation or as part of the gastrointestinal syndrome with IFL. European investigators use the following approach: Patients are provided with a supply of loperamide and a prescription for an oral fluoroquinolone prior to the initiation of treatment. They are instructed that if delayed diarrhea occurs, they should begin taking loperamide 2 mg orally every 2 hours (4 mg orally every 4 hours at night) and continue until they are diarrhea-free for at least 12 hours. If the diarrhea persists for more than 24 hours despite loperamide, they should begin taking the oral fluoroquinolone and continue it for 7 days. If the diarrhea persists for longer than 48 hours, they should stop the loperamide and be hospitalized for parenteral hydration.[12] Oral fluoroquinolone treatment should also initiated in patients who develop an absolute neutrophil count (ANC) less than 500/μL, (even in the absence of fever or diarrhea) or a fever that occurs in the setting of diarrhea (even without neutropenia). Patients must undergo frequent clinical evaluation by a nurse or physician until resolution of the syndrome. Any decision regarding hospitalization should be based upon the patient's clinical status and the physician's ability to follow the patient closely as an outpatient.

4. Appropriate antibiotics should be initiated in any patient hospitalized with prolonged diarrhea, regardless of neutrophil count, and should be continued until resolution of diarrhea. Delayed initiation of antibiotics, premature discontinuation of antibiotics, or selection of inappropriate antibiotics occurred in a number of patients reviewed and is likely to have contributed to their deaths.

5. Physicians should consider grade and duration of toxicity, need and use of supportive care, impact on performance status, and interval since resolution of toxicity in the decision to administer a scheduled dose of IFL chemotherapy. To the extent possible, protocols should incorporate these elements in dose modification criteria.

6. Patients experiencing significant treatment-related diarrhea should not receive IFL chemotherapy. The toxicity should be considered resolved only if the patient has been diarrhea-free or restored to baseline bowel function for at least 24 hours without the use of antidiarrheals or antibiotics.

7. Abdominal cramping should be considered equivalent to diarrhea. If grade 2 abdominal cramping occurs, treatment should be halted until the cramping has fully resolved.

8. Blood tests should be obtained no more than 48 hours prior to scheduled treatment. Attention should be given to the trend of ANC. If it is falling rapidly, then the protocol should allow the physician to pause treatment even if the ANC is adequate for the patient to receive treatment.

9. Changes in electrolytes, including hyponatremia or hypernatremia, hypokalemia, and/or metabolic acidosis, may reflect early physiologic consequences of IFL-induced toxicity. Patients with perturbations in serum sodium, potassium, and/or bicarbonate, even without concomitant elevations in BUN or creatinine, should be carefully evaluated for dehydration and receive aggressive medical management, including fluid and electrolyte replacement.

10. Based on the experience in these and other colorectal cancer clinical trials, older individuals should be followed especially closely.

NOTE ADDED IN PROOF

Data available from the original trial reported by Douillard et al[2] in patients with advanced-stage disease and from ongoing adjuvant colon cancer studies (PETACC-3, E. Van Cutsem, personal communication) report treatment-associated death rates of well below 1% for irinotecan + infusional 5-FU and leucovorin regimens. The reasons for the apparent discrepancy between death rates in those studies and the CALGB and NCCTG studies, including drug administration schedule, should be evaluated further. This information should be considered in the design of future colon cancer adjuvant studies and when considering treatment options for patients with metastatic colorectal cancer who are not enrolled onto a clinical trial.

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APPENDIX

Review Panel Membership: Mace L. Rothenberg, MD, (Chairman), Vanderbilt-Ingram Cancer Center, Nashville, TN; Neal J. Meropol, MD, Fox Chase Cancer Center, Philadelphia, PA; Elizabeth A. Poplin, MD, Cancer Institute of New Jersey, New Brunswick, NJ; Eric Van Cutsem, MD, University Hospital Gasthuisberg, Leuven, Belgium; Scott Wadler, MD, Albert Einstein College of Medicine, Bronx, NY

REFERENCES

1. Saltz LB, Cox JV, Blanke C, et al: Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 543:905-912, 2000

2. Douillard JY, Cunningham D, Roth AD, et al: Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: A multicentre randomised trial. Lancet 355:1041-1047, 2000

3. Morton RF, Goldberg RM, Sargent DJ, et al: Oxaliplatin or CPT-11 combined with 5FU/Leucovorin in advanced colorectal cancer: An NCCTG/CALGB study. Proc Am Soc Clin Oncol 20:125a, 2001 (abstr 495)

4. André T, Bensmaine MA, Louvet C, et al: Multicenter Phase II study of bimonthly high-dose leucovorin, fluorouracil infusion, and oxaliplatin for metastatic colorectal cancer resistant to the same leucovorin and fluorouracil regimen. J Clin Oncol 17:3560-3568, 1999

5. Wasserman E, Cuvier C, Lokiec F, et al: Combination of oxaliplatin plus irinotecan in patients with gastrointestinal tumors: Results of two independent Phase I studies with pharmacokinetics. J Clin Oncol 17:1751-1759, 1999

6. Petrelli N, Douglass HO Jr, Herrera L, et al: The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: A prospective randomized Phase III trial. J Clin Oncol 7:1419-1426, 1989

7. Horak I, Miller LL: Letter to Physicians from Pharmacia Corporation. Peapack, NJ, Pharmicia Corp, May 10, 2001

8. de Gramont A, Figer A, Seymour M, et al: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938-2947, 2000

9. Goldberg RM, Hatfield AK, Kahn M, et al: Prospectively randomized North Central Cancer Treatment Group trial of intensive-course fluorouracil combined with the l-isomer of intravenous leucovorin, oral leucovorin, or intravenous leucovorin for the treatment of advanced colorectal cancer. J Clin Oncol 15:3320-3329, 1997

10. Porschen R, Bermann A, Löffler T, et al: Fluorouracil plus leucovorin as effective adjuvant chemotherapy in curatively resected Stage III colon cancer: Results of the trial adjCCA-01. J Clin Oncol 19:1787-1794, 2001

11. Wolmark N, Rockette H, Mamounas E, et al: Clinical trial to assess the relative efficacy of fluorouracil and luecovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: Results from National Surgical Adjuvant Breast and Bowel Project C-04. J Clin Oncol 17:3553-3559, 1999

12. Van Cutsem E, Cunningham D, Ten Bokkel Huinink WW, et al: Clinical activity and benefit of irinotecan (CPT-11) in patients with colorectal cancer truly resistant to 5-fluorouracil (5-FU). Eur J Cancer 35:54-59, 1999

13. Sargent DJ, Goldberg RM, Mahoney MR, et al: Rapid reporting and review of an increased incidence of a known adverse event. J Natl Cancer Inst 92:1011-1013, 2000

APPENDIX C – CURRENT CAMPTOSAR PACKAGE INSERT.

Camptosar®

irinotecan hydrochloride injection

Pharmacia &Upjohn

For Intravenous Use Only

Camptosar
irinotecan
hydrochloride injection

0816907111

Camptosar
irinotecan
hydrochloride injection

0816907111

WARNINGS

CAMPTOSAR Injection should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

CAMPTOSAR can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Both forms of diarrhea may be severe. Early diarrhea (occurring during or shortly after infusion of CAMPTOSAR) may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Early diarrhea and other cholinergic symptoms may be prevented or ameliorated by atropine (see PRECAUTIONS, General). Late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR) can be prolonged, may lead to dehydration and electrolyte imbalance, and can be life threatening. Late diarrhea should be treated promptly with loperamide; patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated (see WARNINGS). Administration of CAMPTOSAR should be interrupted and subsequent doses reduced if severe diarrhea occurs (see DOSAGE AND ADMINISTRATION).

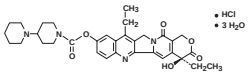
Severe myelosuppression may occur (see WARNINGS).

DESCRIPTION

CAMPTOSAR Injection (irinotecan hydrochloride injection) is an antineoplastic agent of the topoisomerase I inhibitor class. Irinotecan hydrochloride was clinically investigated as CPT-11.

CAMPTOSAR is supplied as a sterile, pale yellow, clear, aqueous solution. It is available in two single-dose sizes: 2 mL-fill vials contain 40 mg irinotecan hydrochloride and 5 mL-fill vials contain 100 mg irinotecan hydrochloride. Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol NF powder, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. CAMPTOSAR is intended for dilution with 5% Dextrose Injection, USP (D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The preferred diluent is 5% Dextrose Injection, USP.

Irinotecan hydrochloride is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata*. The chemical name is ***(S)***-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1***H***-pyrano[3′,4′:6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4′-bipiperidine]-1′-carboxylate, monohydrochloride, trihydrate. Its structural formula is as follows:



Irinotecan Hydrochloride

Irinotecan hydrochloride is a pale yellow to yellow crystalline powder, with the empirical formula $C_{33}H_{38}N_4O_6 \bullet HCl \bullet 3H_2O$ and a molecular weight of 677.19. It is slightly soluble in water and organic solvents.

CLINICAL PHARMACOLOGY

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumor cell lines. In vitro cytotoxicity assays show that the potency of SN-38 relative to irinotecan varies from 2- to 2000-fold. However, the plasma area under the concentration versus time curve (AUC) values for SN-38 are 2% to 8% of irinotecan and SN-38 is 95% bound to plasma proteins compared to approximately 50% bound to plasma proteins for irinotecan (see Pharmacokinetics). The precise contribution of SN-38 to the activity of CAMPTOSAR is thus unknown. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acid pH promotes the formation of the lactone, while a more basic pH favors the hydroxy acid anion form.

Administration of irinotecan has resulted in antitumor activity in mice bearing cancers of rodent origin and in human carcinoma xenografts of various histological types.

Pharmacokinetics

After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours. The half-lives of the lactone (active) forms of irinotecan and SN-38 are similar to those of total irinotecan and SN-38, as the lactone and hydroxy acid forms are in equilibrium.

Over the recommended dose range of 50 to 350 mg/m^2, the AUC of irinotecan increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of irinotecan. Pharmacokinetic parameters for irinotecan and SN-38 following a 90-minute infusion of irinotecan at dose levels of 125 and 340 mg/m^2 determined in two clinical studies in patients with solid tumors are summarized in Table 1.

Table 1. Summary of Mean (± Standard Deviation) Irinotecan and SN-38 Pharmacokinetic Parameters in Patients With Solid Tumors

Dose (mg/m^2)	Irinotecan					SN-38		
	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ (h)	V_z (L/m^2)	CL (L/h/m^2)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ (h)
125 (N=64)	1,660 ±797	10,200 ±3,270	5.8[a] ±0.7	110 ±48.5	13.3 ±6.01	26.3 ±11.9	229 ±108	10.4[a] ±3.1
340 (N=6)	3,392 ±874	20,604 ±6,027	11.7[b] ±1.0	234 ±69.6	13.9 ±4.00	56.0 ±28.2	474 ±245	21.0[b] ±4.3

C_{max} - Maximum plasma concentration

AUC_{0-24} - Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion

$t_{1/2}$ - Terminal elimination half-life

V_z - Volume of distribution of terminal elimination phase

CL - Total systemic clearance

[a] Plasma specimens collected for 24 hours following the end of the 90-minute infusion.

[b] Plasma specimens collected for 48 hours following the end of the 90-minute infusion. Because of the longer collection period, these values provide a more accurate reflection of the terminal elimination half-lives of irinotecan and SN-38.

Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). The plasma protein to which irinotecan and SN-38 predominantly binds is albumin.

Metabolism and Excretion: The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38 subsequently undergoes conjugation to form a glucuronide metabolite. SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines in vitro. The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of irinotecan in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

Camptosar

brand of irinotecan hydrochloride injection

Camptosar
brand of irinotecan hydrochloride injection

Pharmacokinetics in Special Populations

Geriatric: In studies using the weekly schedule, the terminal half-life of irinotecan was 6.0 hours in patients who were 65 years or older and 5.5 hours in patients younger than 65 years. Dose-normalized AUC_{0-24} for SN-38 in patients who were at least 65 years of age was 11% higher than in patients younger than 65 years. No change in the starting dose is recommended for geriatric patients receiving the weekly dosage schedule of irinotecan. The pharmacokinetics of irinotecan given once every 3 weeks has not been studied in the geriatric population; a lower starting dose is recommended in patients 70 years or older based on clinical toxicity experience with this schedule (see DOSAGE AND ADMINISTRATION).

Pediatric: Information regarding the pharmacokinetics of irinotecan is not available.

Gender: The pharmacokinetics of irinotecan do not appear to be influenced by gender.

Race: The influence of race on the pharmacokinetics of irinotecan has not been evaluated.

Hepatic Insufficiency: The influence of hepatic insufficiency on the pharmacokinetic characteristics of irinotecan and its metabolites has not been formally studied. Among patients with known hepatic tumor involvement (a majority of patients), irinotecan and SN-38 AUC values were somewhat higher than values for patients without liver metastases (see PRECAUTIONS).

Renal Insufficiency: The influence of renal insufficiency on the pharmacokinetics of irinotecan has not been evaluated.

Drug-Drug Interactions

In a phase 1 clinical study involving irinotecan, 5-fluorouracil (5-FU), and leucovorin (LV) in 26 patients with solid tumors, the disposition of irinotecan was not substantially altered when the drugs were co-administered. Although the C_{max} and AUC_{0-24} of SN-38, the active metabolite, were reduced (by 14% and 8%, respectively) when irinotecan was followed by 5-FU and LV administration compared with when irinotecan was given alone, this sequence of administration was used in the combination trials and is recommended (see DOSAGE AND ADMINISTRATION). Formal in vivo or in vitro drug interaction studies to evaluate the influence of irinotecan on the disposition of 5-FU and LV have not been conducted.

Possible pharmacokinetic interactions of CAMPTOSAR with other concomitantly administered medications have not been formally investigated.

CLINICAL STUDIES

Irinotecan has been studied in clinical trials in combination with 5-fluorouracil (5-FU) and leucovorin (LV) and as a single agent (see DOSAGE AND ADMINISTRATION). When given as a component of combination-agent treatment, irinotecan was either given with a weekly schedule of bolus 5-FU/LV or with an every-2-week schedule of infusional 5-FU/LV. Weekly and a once-every-3-week dosage schedules were used for the single-agent irinotecan studies. Clinical studies of combination and single-agent use are described below.

First-Line Therapy in Combination with 5-FU/LV for the Treatment of Metastatic Colorectal Cancer

Two phase 3, randomized, controlled, multinational clinical trials support the use of CAMPTOSAR Injection as first-line treatment of patients with metastatic carcinoma of the colon or rectum. In each study, combinations of irinotecan with 5-FU and LV were compared with 5-FU and LV alone. Study 1 compared combination irinotecan/bolus 5-FU/LV therapy given weekly with a standard bolus regimen of 5-FU/LV alone given daily for 5 days every 4 weeks; an irinotecan-alone treatment arm given on a weekly schedule was also included. Study 2 evaluated two different methods of administering infusional 5-FU/LV, with or without irinotecan.

In both studies, the combination of irinotecan/5-FU/LV therapy resulted in significant improvements in objective tumor response rates, time to tumor progression, and survival when compared with 5-FU/LV alone. These differences in survival were observed in spite of second-line therapy in a majority of patients on both arms, including crossover to irinotecan-containing regimens in the control arm. Patient characteristics and major efficacy results are shown in Table 2.

Improvement was noted with irinotecan-based combination therapy relative to 5-FU/LV when response rates and time to tumor progression were examined across the following demographic and disease-related subgroups (age, gender, ethnic origin, performance status, extent of organ involvement with cancer, time from diagnosis of cancer, prior adjuvant therapy, and baseline laboratory abnormalities). Figures 1 and 2 illustrate the Kaplan-Meier survival curves for the comparison of irinotecan/5-FU/LV versus 5-FU/LV in Studies 1 and 2, respectively.

Figure 1. Survival
First-Line Irinotecan/5-FU/LV vs 5-FU/LV
Study 1

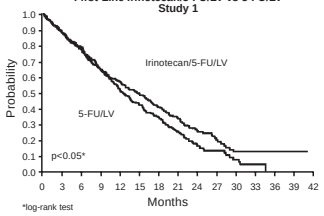
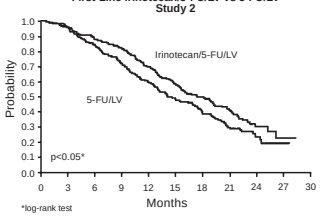


Figure 2. Survival
First-Line Irinotecan/5-FU/LV vs 5-FU/LV
Study 2



Second-Line Treatment for Recurrent or Progressive Metastatic Colorectal Cancer After 5-FU-Based Treatment

Weekly Dosage Schedule

Data from three open-label, single-agent, clinical studies, involving a total of 304 patients in 59 centers, support the use of CAMPTOSAR in the treatment of patients with metastatic cancer of the colon or rectum that has recurred or progressed following treatment with 5-FU-based therapy. These studies were designed to evaluate tumor response rate and do not provide information on actual clinical benefit, such as effects on survival and disease-related symptoms. In each study, CAMPTOSAR was administered in repeated 6-week courses consisting of a 90-minute intravenous infusion once weekly for 4 weeks, followed by a 2-week rest period. Starting doses of CAMPTOSAR in these trials were 100, 125, or 150 mg/m^2, but the 150-mg/m^2 dose was poorly tolerated (due to unacceptably high rates of grade 4 late diarrhea and febrile neutropenia). Study 1 enrolled 48 patients and was conducted by a single investigator at several regional hospitals. Study 2 was a multicenter study conducted by the North Central Cancer Treatment Group. All 90 patients enrolled in Study 2 received a starting dose of 125 mg/m^2. Study 3 was a multicenter study that enrolled 166 patients from 30 institutions. The initial dose in Study 3 was 125 mg/m^2 but was reduced to 100 mg/m^2 because the toxicity seen at the 125-mg/m^2 dose was perceived to be greater than that seen in previous studies. All patients in these studies had metastatic

Table 2. Combination Dosage Schedule: Study Results

	Study 1			Study 2	
	Irinotecan + Bolus 5-FU/LV weekly x 4 q 6 weeks	Bolus 5-FU/LV daily x 5 q 4 weeks	Irinotecan weekly x 4 q 6 weeks	Irinotecan + Infusional 5-FU/LV	Infusional 5-FU/LV
Number of Patients	231	226	226	198	187
Demographics and Treatment Administration					
Female/Male (%)	34/65	45/54	35/64	33/67	47/53
Median Age in years (range)	62 (25-85)	61 (19-85)	61 (30-87)	62 (27-75)	59 (24-75)
Performance Status (%)					
0	39	41	46	51	51
1	46	45	46	42	41
2	15	13	8	7	8
Primary Tumor (%)					
Colon	81	85	84	55	65
Rectum	17	14	15	45	35
Median Time from Diagnosis to Randomization (months, range)	1.9 (0-161)	1.7 (0-203)	1.8 (0.1-185)	4.5 (0-88)	2.7 (0-104)
Prior Adjuvant 5-FU Therapy (%)					
No	89	92	90	74	76
Yes	11	8	10	26	24
Median Duration of Study Treatment[a] (months)	5.5	4.1	3.9	5.6	4.5
Median Relative Dose Intensity (%)[a]					
Irinotecan	72	—	75	87	—
5-FU	71	86	—	86	93
Efficacy Results					
Confirmed Objective Tumor Response Rate[b] (%)	39	21	18	35	22
	(p<0.0001)[c]			(p<0.005)[c]	
Median Time to Tumor Progression[d] (months)	7.0	4.3	4.2	6.7	4.4
	(p=0.004)[d]			(p<0.001)[d]	
Median Survival (months)	14.8	12.6	12.0	17.4	14.1
	(p<0.05)[d]			(p<0.05)[d]	

[a] Study 1: N=225 (irinotecan/5-FU/LV), N=219 (5-FU/LV), N=223 (irinotecan)
Study 2: N=199 (irinotecan/5-FU/LV), N=186 (5-FU/LV)
[b] Confirmed ≥4 to 6 weeks after first evidence of objective response
[c] Chi-square test
[d] Log-rank test

colorectal cancer, and the majority had disease that recurred or progressed following a 5-FU-based regimen administered for metastatic disease. The results of the individual studies are shown in Table 3.

Table 3. Weekly Dosage Schedule: Study Results

	Study			
	1	2	3	
Number of Patients	48	90	64	102
Starting Dose (mg/m^2/wk x 4)	125[a]	125	125	100
Demographics and Treatment Administration				
Female/Male (%)	46/54	36/64	50/50	51/49
Median Age in years (range)	63 (29-78)	63 (32-81)	61 (42-84)	64 (25-84)
Ethnic Origin (%)				
White	79	96	81	91
African American	12	4	11	5
Hispanic	8	0	8	2
Oriental/Asian	0	0	0	2
Performance Status (%)				
0	60	38	59	44
1	38	48	33	51
2	2	14	8	5
Primary Tumor (%)				
Colon	100	71	89	87
Rectum	0	29	11	8
Unknown	0	0	0	5
Prior 5-FU Therapy (%)				
For Metastatic Disease	81	66	73	68
≤6 months after Adjuvant	15	7	27	28
>6 months after Adjuvant	2	16	0	2
Classification Unknown	2	12	0	3
Prior Pelvic/Abdominal Irradiation (%)				
Yes	3	29	0	0
Other	0	9	2	4
None	97	62	98	96
Duration of Treatment with CAMPTOSAR (median, months)	5	4	4	3
Relative Dose Intensity[b] (median %)	74	67	73	81
Efficacy				
Confirmed Objective Response Rate (%)[c] (95% CI)	21 (9.3-32.3)	13 (6.3-20.4)	14 (5.5-22.6)	9 (3.3 -14.3)
Time to Response (median, months)	2.6	1.5	2.8	2.8
Response Duration (median, months)	6.4	5.9	5.6	6.4
Survival (median, months)	10.4	8.1	10.7	9.3
1-Year Survival (%)	46	31	45	43

[a] Nine patients received 150 mg/m^2 as a starting dose; two (22.2%) responded to CAMPTOSAR.
[b] Relative dose intensity for CAMPTOSAR based on planned dose intensity of 100, 83.3, and 66.7 mg/m^2/wk corresponding with 150, 125, and 100 mg/m^2 starting doses, respectively.
[c] Confirmed ≥ 4 to 6 weeks after first evidence of objective response.

In the intent-to-treat analysis of the pooled data across all three studies, 193 of the 304 patients began therapy at the recommended starting dose of 125 mg/m^2. Among these 193 patients, 2 complete and 27 partial responses were observed, for an overall response rate of 15.0% (95% Confidence Interval [CI], 10.0% to 20.1%) at this starting dose. A considerably lower response rate was seen with a starting dose of 100 mg/m^2. The majority of responses were observed within the first two courses of therapy, but responses did occur in later courses of treatment (one response was observed after the eighth course). The median response duration for patients beginning therapy at 125 mg/m^2 was 5.8 months (range, 2.6 to 15.1 months). Of the 304 patients treated in the three studies, response rates to CAMPTOSAR were similar in males and females and among patients older and younger than 65 years. Rates were also similar in patients with cancer of the colon or cancer of the rectum and in patients with single and multiple metastatic sites. The response rate was 18.5% in patients with a performance status of 0 and 8.2% in patients with a performance status of 1 or 2. Patients with a performance status of 3 or 4 have not been studied. Over half of the patients responding to CAMPTOSAR had not responded to prior 5-FU. Patients who had received previous irradiation to the pelvis responded to CAMPTOSAR at approximately the same rate as those who had not previously received irradiation.

Once-Every-3-Week Dosage Schedule

Single-Arm Studies: Data from an open-label, single-agent, single-arm, multicenter, clinical study involving a total of 132 patients support a once every-3-week dosage schedule of irinotecan in the treatment of patients with metastatic cancer of the colon or rectum that recurred or progressed following treatment with 5-FU. Patients received a starting dose of 350 mg/m^2 given by 30-minute intravenous infusion once every 3 weeks. Among the 132 previously treated patients in this trial, the intent-to-treat response rate was 12.1% (95% CI, 7.0% to 18.1%).

Randomized Trials: Two multicenter, randomized, clinical studies further support the use of irinotecan given by the once-every-3-week dosage schedule in patients with metastatic colorectal cancer whose disease has recurred or progressed following prior 5-FU therapy. In the first study, second-line irinotecan therapy plus best supportive care was compared with best supportive care alone. In the second study, second-line irinotecan therapy was compared with infusional 5-FU-based therapy. In both studies, irinotecan was administered intravenously at a starting dose of 350 mg/m^2 over 90 minutes once every 3 weeks. The starting dose was 300 mg/m^2 for patients who were 70 years and older or who had a performance status of 2. The highest total dose permitted was 700 mg. Dose reductions and/or administration delays were permitted in the event of severe hematologic and/or nonhematologic toxicities while on treatment. Best supportive care was provided to patients in both arms of Study 1 and included antibiotics, analgesics, corticosteroids, transfusions, psychotherapy, or any other symptomatic therapy as clinically indicated. Concomitant medications such as antiemetics, atropine, and loperamide were given to patients in the irinotecan arm for prophylaxis and/or management of symptoms from treatment. If late diarrhea persisted for greater than 24 hours despite loperamide, a 7-day course of fluoroquinolone antibiotic prophylaxis was given. Patients in the control arm of the second study received one of the following 5-FU regimens: (1) LV, 200 mg/m^2 IV over 2 hours; followed by 5-FU, 400 mg/m^2 IV bolus; followed by 5-FU, 600 mg/m^2 continuous IV infusion over 22 hours on days 1 and 2 every 2 weeks; (2) 5-FU, 250 to 300 mg/m^2/day protracted continuous IV infusion until toxicity; (3) 5-FU, 2.6 to 3 g/m^2 IV over 24 hours every week for 6 weeks with or without LV, 20 to 500 mg/m^2/day every week IV for 6 weeks with 2-week rest between courses. Patients were to be followed every 3 to 6 weeks for 1 year.

A total of 535 patients were randomized in the two studies at 94 centers. The primary endpoint in both studies was survival. The studies demonstrated a significant overall survival advantage for irinotecan compared with best supportive care (p=0.0001) and infusional 5-FU-based therapy (p=0.035) as shown in Figures 3 and 4. In Study 1, median survival for patients treated with irinotecan was 9.2 months compared with 6.5 months for patients receiving best supportive care. In Study 2, median survival for patients treated with irinotecan was 10.8 months compared with 8.5 months for patients receiving infusional 5-FU-based therapy. Multiple regression analyses determined that patients' baseline characteristics also had a significant effect on survival. When adjusted for performance status and other baseline prognostic factors, survival among patients treated with irinotecan remained significantly longer than in the control populations (p=0.001 for Study 1 and p=0.017 for Study 2). Measurements of pain, performance status, and weight loss were collected prospectively in the two studies; however, the plan for the analysis of these data was defined retrospectively. When comparing irinotecan with best supportive care in Study 1, this analysis showed a statistically significant advantage for irinotecan, with longer time to development of pain (6.9 months versus 2.0 months), time to performance status deterioration (5.7 months versus 3.3 months), and time to > 5% weight loss (6.4 months versus 4.2 months). Additionally, 33.3% (33/99) of patients with a baseline performance status of 1 or 2 showed an improvement in performance status when treated with irinotecan versus 11.3% (7/62) of patients receiving best supportive care (p=0.002). Because of the inclusion of patients with non-measurable disease, intent-to-treat response rates could not be assessed.

Figure 3. Survival
Second-Line Irinotecan vs Best Supportive Care (BSC)
Study 1

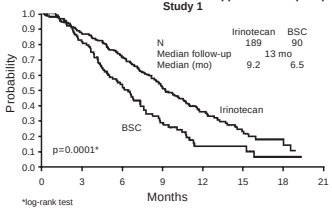


Figure 4. Survival
Second-Line Irinotecan vs Infusional 5-FU
Study 2

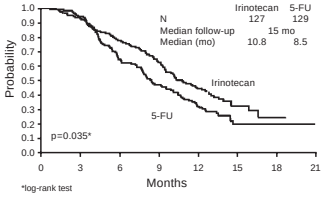


Table 4. Once-Every-3-Week Dosage Schedule: Study Results

	Study 1		Study 2	
	Irinotecan	BSC[a]	Irinotecan	5-FU
Number of Patients	189	90	127	129
Demographics and Treatment Administration				
Female/Male (%)	32/68	42/58	43/57	35/65
Median Age in years (range)	59 (22-75)	62 (34-75)	58 (30-75)	58 (25-75)
Performance Status (%)				
0	47	31	58	54
1	39	46	35	43
2	14	23	8	3
Primary Tumor (%)				
Colon	55	52	57	62
Rectum	45	48	43	38
Prior 5-FU Therapy (%)				
For Metastatic Disease	70	63	58	68
As Adjuvant Treatment	30	37	42	32
Prior Irradiation (%)	26	27	18	20
Duration of Study Treatment (median, months) (Log-rank test)	4.1	—	4.2 (p=0.02)	2.8
Relative Dose Intensity (median %)[b]	94	—	95	81-99
Survival				
Survival (median, months) (Log-rank test)	9.2 (p=0.0001)	6.5	10.8 (p=0.035)	8.5

[a] BSC = best supportive care
[b] Relative dose intensity for irinotecan based on planned dose intensity of 116.7 and 100 mg/m^2/wk corresponding with 350 and 300 mg/m^2 starting doses, respectively.

In the two randomized studies, the EORTC QLQ-C30 instrument was utilized. At the start of each course of

therapy, patients completed a questionnaire consisting of 30 questions, such as "Did pain interfere with daily activities?" (1 = Not at All, to 4 = Very Much) and "Do you have any trouble taking a long walk?" (Yes or No). The answers from the 30 questions were converted into 15 subscales, that were scored from 0 to 100, and the global health status subscale that was derived from two questions about the patient's sense of general well being in the past week. In addition to the global health status subscale, there were five functional (i.e., cognitive, emotional, social, physical, role) and nine symptom (i.e., fatigue, appetite loss, pain assessment, insomnia, constipation, dyspnea, nausea/vomiting, financial impact, diarrhea) subscales. The results as summarized in Table 5 are based on patients' worst post-baseline scores. In Study 1, a multivariate analysis and univariate analyses of the individual subscales were performed and corrected for multivariate testing. Patients receiving irinotecan reported significantly better results for the global health status, on two of five functional subscales, and on four of nine symptom subscales. As expected, patients receiving irinotecan noted significantly more diarrhea than those receiving best supportive care. In Study 2, the multivariate analysis on all 15 subscales did not indicate a statistically significant difference between irinotecan and infusional 5-FU.

Table 5. EORTC QLQ-C30: Mean Worst Post-Baseline Score[a]

QLQ-C30 Subscale	Study 1			Study 2		
	Irinotecan	BSC	p-value	Irinotecan	5-FU	p-value
Global Health Status	47	37	0.03	53	52	0.9
Functional Scales						
Cognitive	77	68	0.07	79	83	0.9
Emotional	68	64	0.4	64	68	0.9
Social	58	47	0.06	65	67	0.9
Physical	60	40	0.0003	66	66	0.9
Role	53	35	0.02	54	57	0.9
Symptom Scales						
Fatigue	51	63	0.03	47	46	0.9
Appetite Loss	37	57	0.0007	35	38	0.9
Pain Assessment	41	56	0.009	38	34	0.9
Insomnia	39	47	0.3	39	33	0.9
Constipation	28	41	0.03	25	19	0.9
Dyspnea	31	40	0.2	25	24	0.9
Nausea/Vomiting	27	29	0.5	25	16	0.09
Financial Impact	22	26	0.5	24	15	0.3
Diarrhea	32	19	0.01	32	22	0.2

[a] For the five functional subscales and global health status subscale, higher scores imply better functioning, whereas, on the nine symptom subscales, higher scores imply more severe symptoms. The subscale scores of each patient were collected at each visit until the patient dropped out of the study.

INDICATIONS AND USAGE

CAMPTOSAR Injection is indicated as a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum. CAMPTOSAR is also indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.

CONTRAINDICATIONS

CAMPTOSAR Injection is contraindicated in patients with a known hypersensitivity to the drug.

WARNINGS

General

Outside of a well-designed clinical study, CAMPTOSAR Injection should not be used in combination with the "Mayo Clinic" regimen of 5-FU/LV (administration for 4-5 consecutive days every 4 weeks) because of reports of increased toxicity, including toxic deaths. CAMPTOSAR should be used as recommended (see DOSAGE AND ADMINISTRATION, Table 10).

Diarrhea

CAMPTOSAR can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or shortly after infusion of CAMPTOSAR) is cholinergic in nature. It is usually transient and only infrequently is severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Early diarrhea and other cholinergic symptoms may be prevented or ameliorated by administration of atropine (see PRECAUTIONS, General, for dosing recommendations for atropine).

Late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR) can be prolonged, may lead to dehydration and electrolyte imbalance, and can be life threatening. Late diarrhea should be treated promptly with loperamide (see PRECAUTIONS, Information for Patients, for dosing recommendations for loperamide). Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. National Cancer Institute (NCI) grade 3 diarrhea is defined as an increase of 7 to 9 stools daily, or incontinence, or severe cramping and NCI grade 4 diarrhea is defined as an increase of ≥10 stools daily, or grossly bloody stool, or need for parenteral support. If grade 3 or 4 late diarrhea occurs, administration of CAMPTOSAR should be delayed until the patient recovers and subsequent doses should be decreased (see DOSAGE AND ADMINISTRATION).

Myelosuppression

Deaths due to sepsis following severe myelosuppression have been reported in patients treated with CAMPTOSAR. Therapy with CAMPTOSAR should be temporarily omitted during a course of therapy if neutropenic fever occurs or if the absolute neutrophil count drops below 1000/mm^3. After the patient recovers to an absolute neutrophil count ≥1000/mm^3, subsequent doses of CAMPTOSAR should be reduced depending upon the level of myelosuppression observed (see DOSAGE AND ADMINISTRATION).

Routine administration of a colony-stimulating factor (CSF) is not necessary, but physicians may wish to consider CSF use in individual patients experiencing significant neutropenia.

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Hypersensitivity

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed.

Colitis/Ileus

Cases of colitis complicated by ulceration, bleeding, ileus or what was described as toxic megacolon have been observed rarely. Cases of ileus without preceding colitis have also been observed rarely.

Renal Impairment/Renal Failure

Rare cases of renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhea.

Pregnancy

CAMPTOSAR may cause fetal harm when administered to a pregnant woman. Radioactivity related to ^{14}C-irinotecan crosses the placenta of rats following intravenous administration of 10 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 3 and 0.5 times, respectively, the corresponding values in patients administered 125 mg/m^2). Administration of 6 mg/kg/day intravenous irinotecan to rats (which in separate studies produced an irinotecan C_{max} and AUC about 2 and 0.2 times, respectively, the corresponding values in patients administered 125 mg/m^2) and rabbits (about one-half the recommended human weekly starting dose on a mg/m^2 basis) during the period of organogenesis, is embryotoxic as characterized by increased post-implantation loss and decreased numbers of live fetuses. Irinotecan was teratogenic in rats at doses greater than 1.2 mg/kg/day (which in separate studies produced an irinotecan C_{max} and AUC about 2/3 and 1/40th, respectively, of the corresponding values in patients administered 125 mg/m^2) and in rabbits at 6.0 mg/kg/day (about one-half the recommended human weekly starting dose on a mg/m^2 basis). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring. There are no adequate and well-controlled studies of irinotecan in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with CAMPTOSAR.

PRECAUTIONS

General

Care of Intravenous Site: CAMPTOSAR Injection is administered by intravenous infusion. Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile water and applications of ice are recommended.

Premedication with Antiemetics: Irinotecan is emetigenic. It is recommended that patients receive premedication with antiemetic agents. In clinical studies of the weekly dosage schedule, the majority of patients received 10 mg of dexamethasone given in conjunction with another type of antiemetic agent, such as a 5-HT^3 blocker (e.g., ondansetron or granisetron). Antiemetic agents should be given on the day of treatment, starting at least 30 minutes before administration of CAMPTOSAR. Physicians should also consider providing patients with an antiemetic regimen (e.g., prochlorperazine) for subsequent use as needed.

Treatment of Cholinergic Symptoms: Prophylactic or therapeutic administration of 0.25 to 1 mg of intravenous or subcutaneous atropine should be considered (unless clinically contraindicated) in patients experiencing rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, abdominal cramping, or diarrhea (occurring during or shortly after infusion of CAMPTOSAR). These symptoms are expected to occur more frequently with higher irinotecan doses.

Patients at Particular Risk: Physicians should exercise particular caution in monitoring the effects of CAMPTOSAR in the elderly (≥65 years) and in patients who had previously received pelvic/abdominal irradiation (see ADVERSE REACTIONS).

The use of CAMPTOSAR in patients with significant hepatic dysfunction has not been established. In clinical trials of either dosing schedule, irinotecan was not administered to patients with serum bilirubin >2.0 mg/dL, or transaminase >3 times the upper limit of normal if no liver metastasis, or transaminase >5 times the upper limit of normal with liver metastasis.

However in clinical trials of the weekly dosage schedule, it has been noted that patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) have had a significantly greater likelihood of experiencing first-course grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50.0% [19/38] versus 17.7% [47/226]; p<0.001). Patients with abnormal glucuronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy with CAMPTOSAR. An association between baseline bilirubin elevations and an increased risk of late diarrhea has not been observed in studies of the weekly dosage schedule.

Information for Patients

Patients and patients' caregivers should be informed of the expected toxic effects of CAMPTOSAR, particularly of its gastrointestinal manifestations, such as nausea, vomiting, and diarrhea. Each patient should be instructed to have loperamide readily available and to begin treatment for late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR) at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. One dosage regimen for loperamide used in clinical trials consisted of the following (Note: This dosage regimen exceeds the usual dosage recommendations for loperamide.): 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. The patient should also be instructed to notify the physician if diarrhea occurs. Premedication with loperamide is not recommended.

The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use.

Patients should consult their physician if vomiting occurs, fever or evidence of infection develops, or if symptoms of dehydration, such as fainting, light-headedness, or dizziness, are noted following therapy

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injection

with CAMPTOSAR.

Patients should be alerted to the possibility of alopecia.

Laboratory Tests

Careful monitoring of the white blood cell count with differential, hemoglobin, and platelet count is recommended before each dose of CAMPTOSAR.

Drug Interactions

The adverse effects of CAMPTOSAR, such as myelosuppression and diarrhea, would be expected to be exacerbated by other antineoplastic agents having similar adverse effects.

Patients who have previously received pelvic/abdominal irradiation are at increased risk of severe myelosuppression following the administration of CAMPTOSAR. The concurrent administration of CAMPTOSAR with irradiation has not been adequately studied and is not recommended.

Lymphocytopenia has been reported in patients receiving CAMPTOSAR, and it is possible that the administration of dexamethasone as antiemetic prophylaxis may have enhanced the likelihood of this effect. However, serious opportunistic infections have not been observed, and no complications have specifically been attributed to lymphocytopenia.

Hyperglycemia has also been reported in patients receiving CAMPTOSAR. Usually, this has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of CAMPTOSAR. It is probable that dexamethasone, given as antiemetic prophylaxis, contributed to hyperglycemia in some patients.

The incidence of akathisia in clinical trials of the weekly dosage schedule was greater (8.5%, 4/47 patients) when prochlorperazine was administered on the same day as CAMPTOSAR than when these drugs were given on separate days (1.3%, 1/80 patients). The 8.5% incidence of akathisia, however, is within the range reported for use of prochlorperazine when given as a premedication for other chemotherapies.

It would be expected that laxative use during therapy with CAMPTOSAR would worsen the incidence or severity of diarrhea, but this has not been studied.

In view of the potential risk of dehydration secondary to vomiting and/or diarrhea induced by CAMPTOSAR, the physician may wish to withhold diuretics during dosing with CAMPTOSAR and, certainly, during periods of active vomiting or diarrhea.

Drug-Laboratory Test Interactions

There are no known interactions between CAMPTOSAR and laboratory tests.

Carcinogenesis, Mutagenesis & Impairment of Fertility

Long-term carcinogenicity studies with irinotecan were not conducted. Rats were, however, administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan once per week for 13 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan C_{max} and AUC that were about 7.0 times and 1.3 times the respective values in patients administered 125 mg/m^2 weekly) and were then allowed to recover for 91 weeks. Under these conditions, there was a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas. Neither irinotecan or SN-38 was mutagenic in the in vitro Ames assay. Irinotecan was clastogenic both in vitro (chromosome aberrations in Chinese hamster ovary cells) and in vivo (micronucleus test in mice). No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan in doses of up to 6 mg/kg/day to rats and rabbits. However, atrophy of male reproductive organs was observed after multiple daily irinotecan doses both in rodents at 20 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 5 and 1 times, respectively, the corresponding values in patients administered 125 mg/m^2 weekly) and dogs at 0.4 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about one-half and 1/15th, respectively, the corresponding values in patients administered 125 mg/m^2 weekly).

Pregnancy

Pregnancy Category D—see WARNINGS.

Nursing Mothers

Radioactivity appeared in rat milk within 5 minutes of intravenous administration of radiolabeled irinotecan and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving therapy with CAMPTOSAR.

Pediatric Use

The safety and effectiveness of CAMPTOSAR in pediatric patients have not been established.

Geriatric Use

Patients greater than 65 years of age should be closely monitored because of a greater risk of late diarrhea in this population (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations and ADVERSE REACTIONS, Overview of Adverse Events). The starting dose of CAMPTOSAR in patients 70 years and older for the once-every-3-week-dosage schedule should be 300 mg/m^2 (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

First-Line Combination Therapy

A total of 955 patients with metastatic colorectal cancer received the recommended regimens of irinotecan in combination with 5-FU/LV, 5-FU/LV alone, or irinotecan alone. In the two phase 3 studies, 370 patients received irinotecan in combination with 5-FU/LV, 362 patients received 5-FU/LV alone, and 223 patients received irinotecan alone. (See Table 10 in DOSAGE AND ADMINISTRATION for recommended combination-agent regimens.)

In Study 1, 49 (7.3%) patients died within 30 days of study treatment: 21 (9.3%) received irinotecan in combination with 5-FU/LV, 15 (6.8%) received 5-FU/LV alone, and 13 (5.8%) received irinotecan alone. Deaths potentially related to treatment occurred in 2 (0.9%) patients who received irinotecan in combination with 5-FU/LV (2 neutropenic fever/sepsis), 3 (1.4%) patients who received 5-FU/LV alone (1 neutropenic fever/sepsis, 1 CNS bleeding during thrombocytopenia, 1 unknown) and 2 (0.9%) patients who received irinotecan alone (2 neutropenic fever). Discontinuations due to adverse events were reported for 17 (7.6%) patients who received irinotecan in combination with 5-FU/LV, 14 (6.4%) patients who received 5-FU/LV alone, and 26 (11.7%) patients who received irinotecan alone.

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In Study 2, 10 (3.5%) patients died within 30 days of study treatment: 6 (4.1%) received irinotecan in combination with 5-FU/LV and 4 (2.8%) received 5-FU/LV alone. There was one potentially treatment-death, which occurred in a patient who received irinotecan in combination with 5-FU/LV (0.7%, neutropenic sepsis). Discontinuations due to adverse events were reported for 9 (6.2%) patients who received irinotecan in combination with 5-FU/LV and 1 (0.7%) patients who received 5-FU/LV alone.

The most clinically significant adverse events (all grades 1-4) for patients receiving irinotecan-based therapy were diarrhea, nausea, vomiting, neutropenia, and alopecia. The most clinically significant adverse events for patients receiving 5-FU/LV therapy were diarrhea, neutropenia, neutropenic fever, and mucositis. In Study 1, grade 4 neutropenia, neutropenic fever (defined as grade 2 fever and grade 4 neutropenia), and mucositis were observed less often with weekly irinotecan/5-FU/LV than with monthly administration of 5-FU/LV.

Tables 6 and 7 list the clinically relevant adverse events reported in Studies 1 and 2, respectively.

Table 6. Study 1: Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies

Adverse Event	Study 1					
	Irinotecan + Bolus 5-FU/LV weekly x 4 q 6 weeks N=225		Bolus 5-FU/LV daily x 5 q 4 weeks N=219		Irinotecan weekly x 4 q 6 weeks N=223	
	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4
TOTAL Adverse Events	100	53.3	100	45.7	99.6	45.7
GASTROINTESTINAL						
Diarrhea						
late	84.9	22.7	69.4	13.2	83.0	31.0
grade 3	—	15.1	—	5.9	—	18.4
grade 4	—	7.6	—	7.3	—	12.6
early	45.8	4.9	31.5	1.4	43.0	6.7
Nausea	79.1	15.6	67.6	8.2	81.6	16.1
Abdominal pain	63.1	14.6	50.2	11.5	67.7	13.0
Vomiting	60.4	9.7	46.1	4.1	62.8	12.1
Anorexia	34.2	5.8	42.0	3.7	43.9	7.2
Constipation	41.3	3.1	31.5	1.8	32.3	0.4
Mucositis	32.4	2.2	76.3	16.9	29.6	2.2
HEMATOLOGIC						
Neutropenia	96.9	53.8	98.6	66.7	96.4	31.4
grade 3	—	29.8	—	23.7	—	19.3
grade 4	—	24.0	—	42.5	—	12.1
Leukopenia	96.9	37.8	98.6	23.3	96.4	21.5
Anemia	96.9	8.4	98.6	5.5	96.9	4.5
Neutropenic fever	—	7.1	—	14.6	—	5.8
Thrombocytopenia	96.0	2.6	98.6	2.7	96.0	1.7
Neutropenic infection	—	1.8	—	0	—	2.2
BODY AS A WHOLE						
Asthenia	70.2	19.5	64.4	11.9	69.1	13.9
Pain	30.7	3.1	26.9	3.6	22.9	2.2
Fever	42.2	1.7	32.4	3.6	43.5	0.4
Infection	22.2	0	16.0	1.4	13.9	0.4
METABOLIC & NUTRITIONAL						
↑ Bilirubin	87.6	7.1	92.2	8.2	83.9	7.2
DERMATOLOGIC						
Exfoliative dermatitis	0.9	0	3.2	0.5	0	0
Rash	19.1	0	26.5	0.9	14.3	0.4
Alopecia[a]	43.1	—	26.5	—	46.1	—
RESPIRATORY						
Dyspnea	27.6	6.3	16.0	0.5	22.0	2.2
Cough	26.7	1.3	18.3	0	20.2	0.4
Pneumonia	6.2	2.7	1.4	1.0	3.6	1.3
NEUROLOGIC						
Dizziness	23.1	1.3	16.4	0	21.1	1.8
Somnolence	12.4	1.8	4.6	1.8	9.4	1.3
Confusion	7.1	1.8	4.1	0	2.7	0
CARDIOVASCULAR						
Vasodilation	9.3	0.9	5.0	0	9.0	0
Hypotension	5.8	1.3	2.3	0.5	5.8	1.7
Thrombophlebitis	5.3	2.7	6.8	3.2	3.1	1.8
Pulmonary embolus	2.7	2.7	1.4	1.4	0.9	0.4
Myocardial infarction	1.3	1.3	0	0	0.4	0.4

[a] Complete hair loss = Grade 2

Table 7. Study 2: Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies

Adverse Event	Study 2			
	Irinotecan + 5-FU/LV Infusional d 1&2 q 2 weeks N=145		5-FU/LV Infusional d 1&2 q 2 weeks N=143	
	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4
TOTAL Adverse Events	100	72.4	100	39.2
GASTROINTESTINAL				
Diarrhea				
late	68.3	14.5	44.8	6.3
grade 3	—	10.3	—	4.2
grade 4	—	4.1	—	2.1
Cholinergic syndrome[a]	28.3	1.4	0.7	0
Nausea	66.9	2.1	55.2	3.5
Abdominal pain	17.2	2.1	16.8	0.7
Vomiting	44.1	3.5	32.2	2.8
Anorexia	35.2	2.1	18.9	0.7
Constipation	30.3	0.7	25.2	1.4
Mucositis	40.0	4.1	26.7	2.8
HEMATOLOGIC				
Neutropenia	82.5	46.2	47.9	13.4
grade 3	—	36.4	—	12.7
grade 4	—	9.8	—	0.7
Leukopenia	81.3	17.4	42.0	3.5
Anemia	97.2	2.1	90.0	2.1
Neutropenic fever	—	9.3	—	2.3
Thrombocytopenia	32.6	0	32.2	0
Neutropenic infection	—	2.1	—	0
BODY AS A WHOLE				
Asthenia	57.9	9.0	48.3	4.2
Pain	64.1	9.7	61.5	8.4
Fever	22.1	0.7	25.9	0.7
Infection	35.9	7.6	33.6	3.5
METABOLIC & NUTRITIONAL				
↑ Bilirubin	19.1	3.5	35.9	10.6
DERMATOLOGIC				
Hand & foot syndrome	10.3	0.7	12.6	0.7
Cutaneous signs	17.2	0.7	20.3	0
Alopecia[b]	56.6	—	16.8	—
RESPIRATORY				
Dyspnea	9.7	1.4	4.9	0
CARDIOVASCULAR				
Hypotension	3.4	1.4	0.7	0

[a] Includes rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, abdominal cramping or diarrhea (occurring during or shortly after infusion of irinotecan)
[b] Complete hair loss = Grade 2

Second-Line Single-Agent Therapy

Weekly Dosage Schedule

In three clinical studies evaluating the weekly dosage schedule, 304 patients with metastatic carcinoma of the colon or rectum that had recurred or progressed following 5-FU-based therapy were treated with CAMPTOSAR. Seventeen of the patients died within 30 days of the administration of CAMPTOSAR; in five cases (1.6%, 5/304), the deaths were potentially drug-related. These five patients experienced a constellation of medical events that included known effects of CAMPTOSAR. One of these patients died of neutropenic sepsis without fever. Neutropenic fever occurred in nine (3.0%) other patients; these patients recovered with supportive care.

One hundred nineteen (39.1%) of the 304 patients were hospitalized a total of 156 times because of adverse events; 81 (26.6%) patients were hospitalized for events judged to be related to administration of CAMPTOSAR. The primary reasons for drug-related hospitalization were diarrhea, with or without nausea and/or vomiting (18.4%); neutropenia/leukopenia, with or without diarrhea and/or fever (8.2%); and nausea and/or vomiting (4.9%).

Adjustments in the dose of CAMPTOSAR were made during the course of treatment and for subsequent courses based on individual patient tolerance. The first dose of at least one course of CAMPTOSAR was reduced for 67% of patients who began the studies at the 125-mg/m^2 starting dose. Within-course dose reductions were required for 32% of the courses initiated at the 125-mg/m^2 dose level. The most common reasons for dose reduction were late diarrhea, neutropenia, and leukopenia. Thirteen (4.3%) patients discontinued treatment with CAMPTOSAR because of adverse events. The adverse events in Table 8 are based on the experience of the 304 patients enrolled in the three studies described in the CLINICAL STUDIES, Studies Evaluating the Weekly Dosage Schedule, section.

Table 8. Adverse Events Occurring in >10% of 304 Previously Treated Patients with Metastatic Carcinoma of the Colon or Rectum

Body System & Event	% of Patients Reporting	
	NCI Grades 1-4	NCI Grades 3 & 4
GASTROINTESTINAL		
Diarrhea (late)[a]	88	31
7-9 stools/day (grade 3)	—	(16)
≥10 stools/day (grade 4)	—	(14)
Nausea	86	17
Vomiting	67	12
Anorexia	55	6
Diarrhea (early)[b]	51	8
Constipation	30	2
Flatulence	12	0
Stomatitis	12	1
Dyspepsia	10	0
HEMATOLOGIC		
Leukopenia	63	28
Anemia	60	7
Neutropenia	54	26
500 to <1000/mm^3 (grade 3)	—	(15)
<500/mm^3 (grade 4)	—	(12)
BODY AS A WHOLE		
Asthenia	76	12
Abdominal cramping/pain	57	16
Fever	45	1
Pain	24	2
Headache	17	1
Back pain	14	2
Chills	14	0
Minor Infection[c]	14	0
Edema	10	1
Abdominal Enlargement	10	0
METABOLIC & NUTRITIONAL		
↓Body weight	30	1
Dehydration	15	4
↑Alkaline phosphatase	13	4
↑SGOT	10	1
DERMATOLOGIC		
Alopecia	60	NA[d]
Sweating	16	0
Rash	13	1
RESPIRATORY		
Dyspnea	22	4
↑Coughing	17	0
Rhinitis	16	0
NEUROLOGIC		
Insomnia	19	0
Dizziness	15	0
CARDIOVASCULAR		
Vasodilation (Flushing)	11	0

[a] Occurring >24 hours after administration of CAMPTOSAR
[b] Occurring ≤24 hours after administration of CAMPTOSAR
[c] Primarily upper respiratory infections
[d] Not applicable; complete hair loss = NCI grade 2

Once-Every-3-Week Dosage Schedule

A total of 535 patients with metastatic colorectal cancer whose disease had recurred or progressed following prior 5-FU therapy participated in the two phase 3 studies: 316 received irinotecan, 129 received 5-FU, and 90 received best supportive care. Eleven (3.5%) patients treated with irinotecan died within 30 days of treatment. In three cases (1%, 3/316), the deaths were potentially related to irinotecan treatment and were attributed to neutropenic infection, grade 4 diarrhea, and asthenia, respectively. One (0.8%, 1/129) patient treated with 5-FU died within 30 days of treatment; this death was attributed to grade 4 diarrhea.

Hospitalizations due to serious adverse events (whether or not related to study treatment) occurred at least once in 60% (188/316) of patients who received irinotecan, 63% (57/90) who received best supportive care, and 39% (50/129) who received 5-FU-based therapy. Eight percent of patients treated with irinotecan and 7% treated with 5-FU-based therapy discontinued treatment due to adverse events.

Of the 316 patients treated with irinotecan, the most clinically significant adverse events (all grades, 1-4) were diarrhea (84%), alopecia (72%), nausea (70%), vomiting (62%), cholinergic symptoms (47%), and neutropenia (30%). Table 9 lists the grade 3 and 4 adverse events reported in the patients enrolled to all treatment arms of the two studies described in the CLINICAL STUDIES, Studies Evaluating the Once-Every-3-Week Dosage Schedule, section.

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Table 9. Percent of Patients Experiencing Grade 3 & 4 Adverse Events in Comparative Studies of Once-Every-3-Week Irinotecan Therapy

Adverse Event	Study 1		Study 2	
	Irinotecan N=189	BSC[a] N=90	Irinotecan N=127	5-FU N=129
TOTAL Grade 3/4 Adverse Events	79	67	69	54
GASTROINTESTINAL				
Diarrhea	22	6	22	11
Vomiting	14	8	14	5
Nausea	14	3	11	4
Abdominal pain	14	16	9	8
Constipation	10	8	8	6
Anorexia	5	7	6	4
Mucositis	2	1	2	5
HEMATOLOGIC				
Leukopenia/Neutropenia	22	0	14	2
Anemia	7	6	6	3
Hemorrhage	5	3	1	3
Thrombocytopenia	1	0	4	2
Infection				
without grade 3/4 neutropenia	8	3	1	4
with grade 3/4 neutropenia	1	0	2	0
Fever				
without grade 3/4 neutropenia	2	1	2	0
with grade 3/4 neutropenia	2	0	4	2
BODY AS A WHOLE				
Pain	19	22	17	13
Asthenia	15	19	13	12
METABOLIC & NUTRITIONAL				
Hepatic[b]	9	7	9	6
DERMATOLOGIC				
Hand & foot syndrome	0	0	0	5
Cutaneous signs[c]	2	0	1	3
RESPIRATORY[d]	10	8	5	7
NEUROLOGIC[e]	12	13	9	4
CARDIOVASCULAR[f]	9	3	4	2
OTHER[g]	32	28	12	14

[a] BSC = best supportive care
[b] Hepatic includes events such as ascites and jaundice
[c] Cutaneous signs include events such as rash
[d] Respiratory includes events such as dyspnea and cough
[e] Neurologic includes events such as somnolence
[f] Cardiovascular includes events such as dysrhythmias, ischemia, and mechanical cardiac dysfunction
[g] Other includes events such as accidental injury, hepatomegaly, syncope, vertigo, and weight loss

Overview of Adverse Events

Gastrointestinal: Nausea, vomiting, and diarrhea are common adverse events following treatment with CAMPTOSAR and can be severe. When observed, nausea and vomiting usually occur during or shortly after infusion of CAMPTOSAR. In the clinical studies testing the every 3-week-dosage schedule, the median time to the onset of late diarrhea was 5 days after irinotecan infusion. In the clinical studies evaluating the weekly dosage schedule, the median time to onset of late diarrhea was 11 days following administration of CAMPTOSAR. For patients starting treatment at the 125-mg/m^2 weekly dose, the median duration of any grade of late diarrhea was 3 days. Among those patients treated at the 125-mg/m^2 weekly dose who experienced grade 3 or 4 late diarrhea, the median duration of the entire episode of diarrhea was 7 days. The frequency of grade 3 or 4 late diarrhea was somewhat greater in patients starting treatment at 125 mg/m^2 than in patients given a 100-mg/m^2 weekly starting dose (34% [65/193] versus 23% [24/102]; p=0.08). The frequency of grade 3 and 4 late diarrhea by age was significantly greater in patients ≥65 years than in patients <65 years (40% [53/133] versus 23% [40/171]; p=0.002). In one study of the weekly dosage treatment, the frequency of grade 3 and 4 late diarrhea was significantly greater in male than in female patients (43% [25/58] versus 16% [5/32]; p=0.01), but there were no gender differences in the frequency of grade 3 and 4 late diarrhea in the other two studies of the weekly dosage treatment schedule. Colonic ulceration, sometimes with gastrointestinal bleeding, has been observed in association with administration of CAMPTOSAR.

Hematology: CAMPTOSAR commonly causes neutropenia, leukopenia (including lymphocytopenia), and anemia. Serious thrombocytopenia is uncommon. When evaluated in the trials of weekly administration, the frequency of grade 3 and 4 neutropenia was significantly higher in patients who received previous pelvic/abdominal irradiation than in those who had not received such irradiation (48% [13/27] versus 24% [67/277]; p=0.04). In these same studies, patients with baseline serum total bilirubin levels of 1.0 mg/dL or more also had a significantly greater likelihood of experiencing first-course grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50% [19/38] versus 18% [47/266]; p<0.001). There were no significant differences in the frequency of grade 3 and 4 neutropenia by age or gender. In the clinical studies evaluating the weekly dosage schedule, neutropenic fever (concurrent NCI grade 4 neutropenia and fever of grade 2 or greater) occurred in 3% of the patients; 6% of patients received G-CSF for the treatment of neutropenia. NCI grade 3 or 4 anemia was noted in 7% of the patients receiving weekly treatment; blood transfusions were given to 10% of the patients in these trials.

Body as a Whole: Asthenia, fever, and abdominal pain are generally the most common events of this type.

Cholinergic Symptoms: Patients may have cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping and early diarrhea. If these symptoms occur, they manifest during or shortly after drug infusion. They are thought to be related to the anticholinesterase activity of the irinotecan parent compound and are expected to occur more frequently with higher irinotecan doses.

Hepatic: In the clinical studies evaluating the weekly dosage schedule, NCI grade 3 or 4 liver enzyme abnormalities were observed in fewer than 10% of patients. These events typically occur in patients with known hepatic metastases.

Dermatologic: Alopecia has been reported during treatment with CAMPTOSAR. Rashes have also been reported but did not result in discontinuation of treatment.

Respiratory: Severe pulmonary events are infrequent. In the clinical studies evaluating the weekly dosage sched-

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ule, NCI grade 3 or 4 dyspnea was reported in 4% of patients. Over half the patients with dyspnea had lung metastases; the extent to which malignant pulmonary involvement or other preexisting lung disease may have contributed to dyspnea in these patients is unknown.

Neurologic: Insomnia and dizziness can occur, but are not usually considered to be directly related to the administration of CAMPTOSAR. Dizziness may sometimes represent symptomatic evidence of orthostatic hypotension in patients with dehydration.

Cardiovascular: Vasodilation (flushing) may occur during administration of CAMPTOSAR. Bradycardia may also occur, but has not required intervention. These effects have been attributed to the cholinergic syndrome sometimes observed during or shortly after infusion of CAMPTOSAR.

Other Non-U.S. Clinical Trials

Irinotecan has been studied in over 1100 patients in Japan. Patients in these studies had a variety of tumor types, including cancer of the colon or rectum, and were treated with several different doses and schedules. In general, the types of toxicities observed were similar to those seen in U.S. trials with CAMPTOSAR. There is some information from Japanese trials that patients with considerable ascites or pleural effusions were at increased risk for neutropenia or diarrhea. A potentially life-threatening pulmonary syndrome, consisting of dyspnea, fever, and a reticulonodular pattern on chest x-ray, was observed in a small percentage of patients in early Japanese studies. The contribution of irinotecan to these preliminary events was difficult to assess because these patients also had lung tumors and some had preexisting nonmalignant pulmonary disease. As a result of these observations, however, clinical studies in the United States have enrolled few patients with compromised pulmonary function, significant ascites, or pleural effusions.

Post-Marketing Experience

The following events have been identified during post-marketing use of CAMPTOSAR in clinical practice. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to CAMPTOSAR, or a combination of these factors, include: rare cases of colitis complicated by ulceration, bleeding, ileus, or what was described as toxic megacolon; rare cases of ileus without preceding colitis; and rare cases of renal impairment and acute renal failure, generally in patients who became volume depleted from severe vomiting and/or diarrhea (see WARNINGS).

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed (see WARNINGS).

OVERDOSAGE

In U.S. phase 1 trials, single doses of up to 345 mg/m^2 of irinotecan were administered to patients with various cancers. Single doses of up to 750 mg/m^2 of irinotecan have been given in non-U.S. trials. The adverse events in these patients were similar to those reported with the recommended dosage and regimen. There is no known antidote for overdosage of CAMPTOSAR. Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat any infectious complications.

DOSAGE AND ADMINISTRATION

Combination-Agent Dosage

Dosage Regimens

CAMPTOSAR Injection in Combination with 5-Fluorouracil (5-FU) and Leucovorin (LV)

CAMPTOSAR should be administered as an intravenous infusion over 90 minutes (see Preparation of Infusion Solution). For all regimens, the dose of LV should be administered immediately after CAMPTOSAR, with the administration of 5-FU to occur immediately after receipt of LV. CAMPTOSAR should be used as recommended; the currently recommended regimens are shown in Table 10.

Dosing for patients with bilirubin >2 mg/dL cannot be recommended since such patients were not included in clinical studies. It is recommended that patients receive premedication with antiemetic agents. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms. See PRECAUTIONS, General.

Dose Modifications

Patients should be carefully monitored for toxicity, and doses of CAMPTOSAR and 5-FU should be modified as necessary to accommodate individual patient tolerance to treatment. Based on the recommended dose-levels described in Table 10, Combination-Agent Dosage Regimens & Dose Modifications, subsequent doses should be adjusted as suggested in Table 11, Recommended Dose Modifications for Combination Schedules. All dose modifications should be based on the worst preceding toxicity.

A new course of therapy should not begin until the toxicity has recovered to NCI grade 1 or less. Treatment may be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity. If the patient has not recovered, consideration should be given to discontinuing therapy. Provided intolerable toxicity does not develop, treatment with additional courses of CAMPTOSAR/5-FU/LV may be continued indefinitely as long as patients continue to experience clinical benefit.

Single-Agent Dosage Schedules

Dosage Regimens

CAMPTOSAR should be administered as an intravenous infusion over 90 minutes for both the weekly and once-every-3-week dosage schedules (see Preparation of Infusion Solution). Single-agent dosage regimens are shown in Table 12.

Table 10. Combination-Agent Dosage Regimens & Dose Modifications[a]

Regimen 1 6-wk course with bolus 5-FU/LV (next course begins on day 43)	CAMPTOSAR LV 5-FU	125 mg/m^2 IV over 90 min, d 1,8,15,22 20 mg/m^2 IV bolus, d 1,8,15,22 500 mg/m^2 IV bolus, d 1,8,15,22		
		Starting Dose & Modified Dose Levels (mg/m^2)		
		Starting Dose	Dose Level -1	Dose Level -2
	CAMPTOSAR LV 5-FU	125 20 500	100 20 400	75 20 300
Regimen 2 6-wk course with infusional 5-FU/LV (next course begins on day 43)	CAMPTOSAR LV 5-FU Bolus 5-FU Infusion[b]	180 mg/m^2 IV over 90 min, d 1,15,29 200 mg/m^2 IV over 2 h, d 1,2,15,16,29,30 400 mg/m^2 IV bolus, d 1,2,15,16,29,30 600 mg/m^2 IV over 22 h, d 1,2,15,16,29,30		
		Starting Dose & Modified Dose Levels (mg/m^2)		
		Starting Dose	Dose Level -1	Dose Level -2
	CAMPTOSAR LV 5-FU Bolus 5-FU Infusion[b]	180 200 400 600	150 200 320 480	120 200 240 360

[a] Dose reductions beyond dose level –2 by decrements of ≈20% may be warranted for patients continuing to experience toxicity. Provided intolerable toxicity does not develop, treatment with additional courses may be continued indefinitely as long as patients continue to experience clinical benefit.

[b] Infusion follows bolus administration.

Table 11. Recommended Dose Modifications for CAMPTOSAR/5-Fluorouracil (5-FU)/Leucovorin (LV) Combination Schedules

A new course of therapy should not begin until the granulocyte count has recovered to ≥1500/mm^3, and the platelet count has recovered to ≥100,000/mm^3, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing therapy.

Toxicity NCI CTC grade[a] (Value)	During a Course of Therapy	At the Start of Subsequent Courses of Therapy[b]
No toxicity	Maintain dose level	Maintain dose level
Neutropenia 1 (1500 to 1999/mm^3) 2 (1000 to 1499/mm^3) 3 (500 to 999/mm^3) 4 (< 500/mm^3) Neutropenic fever (grade 4 neutropenia & ≥ grade 2 fever)	Maintain dose level ↓ 1 dose level Omit dose, then ↓ 1 dose level when resolved to ≤ grade 2 Omit dose, then ↓ 2 dose levels when resolved to ≤ grade 2 Omit dose, then ↓ 2 dose levels when resolved	Maintain dose level Maintain dose level ↓ 1 dose level ↓ 2 dose levels ↓ 2 dose levels
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia during a course of therapy and at the start of subsequent courses of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea 1 (2-3 stools/day > pretx[c]) 2 (4-6 stools/day > pretx) 3 (7-9 stools/day > pretx) 4 (≥10 stools/day > pretx)	Maintain dose level ↓ 1 dose level Omit dose, then ↓ 1 dose level when resolved to ≤ grade 2 Omit dose, then ↓ 2 dose levels when resolved to ≤ grade 2	Maintain dose level Maintain dose level ↓ 1 dose level ↓ 2 dose levels
Other nonhematologic toxicities 1 2 3 4	Maintain dose level ↓ 1 dose level Omit dose, then ↓ 1 dose level when resolved to ≤ grade 2 Omit dose, then ↓ 2 dose levels when resolved to ≤ grade 2 *For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR*	Maintain dose level Maintain dose level ↓ 1 dose level ↓ 2 dose levels *For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR*

[a] National Cancer Institute Common Toxicity Criteria

[b] Relative to the starting dose used in the previous course

[c] Pretreatment

A reduction in the starting dose by one dose level of CAMPTOSAR may be considered for patients with any of the following conditions: age ≥65 years, prior pelvic/abdominal radiotherapy, performance status of 2, or increased bilirubin levels. Dosing for patients with bilirubin >2 mg/dL cannot be recommended since such patients were not included in clinical studies.

It is recommended that patients receive premedication with antiemetic agents. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms. See PRECAUTIONS, General.

Dose Modifications

Patients should be carefully monitored for toxicity and doses of CAMPTOSAR should be modified as necessary to accommodate individual patient tolerance to treatment. Based on recommended dose-levels described in Table 12, Single-Agent Regimens of CAMPTOSAR and Dose Modifications, subsequent doses should be adjusted as suggested in Table 13, Recommended Dose Modifications for Single-Agent Schedules. All dose modifications should be based on the worst preceding toxicity.

A new course of therapy should not begin until the toxicity has recovered to NCI grade 1 or less. Treatment may be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity. If the patient has not recovered, consideration should be given to discontinuing this combination therapy. Provided intolerable toxicity does not develop, treatment with additional courses of CAMPTOSAR may be continued indefinitely as long as patients continue to experience clinical benefit.

Table 12. Single-Agent Regimens of CAMPTOSAR and Dose Modifications

Weekly Regimen[a]	125 mg/m² IV over 90 min, d 1,8,15,22 then 2-wk rest		
	Starting Dose & Modified Dose Levels[c] (mg/m²)		
	Starting Dose	Dose Level -1	Dose Level -2
	125	100	75
Once-Every-3-Week Regimen[b]	350 mg/m² IV over 90 min, once every 3 wks[c]		
	Starting Dose & Modified Dose Levels (mg/m²)		
	Starting Dose	Dose Level -1	Dose Level -2
	350	300	250

[a] Subsequent doses may be adjusted as high as 150 mg/m² or to as low as 50 mg/m² in 25 to 50 mg/m² decrements depending upon individual patient tolerance.
[b] Subsequent doses may be adjusted as low as 200 mg/m² in 50 mg/m² decrements depending upon individual patient tolerance.
[c] Provided intolerable toxicity does not develop, treatment with additional courses may be continued indefinitely as long as patients continue to experience clinical benefit.

Table 13. Recommended Dose Modifications for Single-Agent Schedules[a]

A new course of therapy should not begin until the granulocyte count has recovered to ≥1500/mm³, and the platelet count has recovered to ≥100,000/mm³, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing CAMPTOSAR.

Worst Toxicity NCI Grade[b] (Value)	During a Course of Therapy	At the Start of the Next Courses of Therapy (After Adequate Recovery), Compared with the Starting Dose in the Previous Course[a]	
	Weekly	Weekly	Once Every 3 Weeks
No toxicity	Maintain dose level	↑25 mg/m² up to a maximum dose of 150 mg/m²	Maintain dose level
Neutropenia			
1 (1500 to 1999/mm³)	Maintain dose level	Maintain dose level	Maintain dose level
2 (1000 to 1499/mm³)	↓25 mg/m²	Maintain dose level	Maintain dose level
3 (500 to 999/mm³)	Omit dose, then ↓25 mg/m² when resolved to ≤ grade 2	↓25 mg/m²	↓50 mg/m²
4 (<500/mm³)	Omit dose, then ↓50 mg/m² when resolved to ≤ grade 2	↓50 mg/m²	↓50 mg/m²
Neutropenic fever (grade 4 neutropenia & ≥ grade 2 fever)	Omit dose, then ↓50 mg/m² when resolved	↓50 mg/m²	↓50 mg/m²
Other hematologic toxicities	Dose modifications for leukopenia, thrombocytopenia, and anemia during a course of therapy and at the start of subsequent courses of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.		
Diarrhea			
1 (2-3 stools/day > pretx[c])	Maintain dose level	Maintain dose level	Maintain dose level
2 (4-6 stools/day > pretx)	↓25 mg/m²	Maintain dose level	Maintain dose level
3 (7-9 stools/day > pretx)	Omit dose, then ↓25 mg/m² when resolved to ≤ grade 2	↓25 mg/m²	↓50 mg/m²
4 (≥ 10 stools/day > pretx)	Omit dose, then ↓50 mg/m² when resolved to ≤ grade 2	↓50 mg/m²	↓50 mg/m²
Other nonhematologic toxicities			
1	Maintain dose level	Maintain dose level	Maintain dose level
2	↓25 mg/m²	↓25 mg/m²	↓50 mg/m²
3	Omit dose, then ↓25 mg/m² when resolved to ≤ grade 2	↓25 mg/m²	↓50 mg/m²
4	Omit dose, then ↓50 mg/m² when resolved to ≤ grade 2	↓50 mg/m²	↓50 mg/m²

[a] All dose modifications should be based on the worst preceding toxicity
[b] National Cancer Institute Common Toxicity Criteria
[c] Pretreatment

Preparation & Administration Precautions

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions prepared from CAMPTOSAR Injection. The use of gloves is recommended. If a solution of CAMPTOSAR contacts the skin, wash the skin immediately and thoroughly with soap and water. If CAMPTOSAR contacts the mucous membranes, flush thoroughly with water. Several published guidelines for handling and disposal of anticancer agents are available.[1-7]

Preparation of Infusion Solution

Inspect vial contents for particulate matter and repeat inspection when drug product is withdrawn from vial into syringe.

CAMPTOSAR Injection must be diluted prior to infusion. CAMPTOSAR should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 to 2.8 mg/mL. In most clinical trials, CAMPTOSAR was administered in 250 mL to 500 mL of 5% Dextrose Injection, USP.

The solution is physically and chemically stable for up to 24 hours at room temperature (approximately 25°C) and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. Freezing CAMPTOSAR and admixtures of CAMPTOSAR may result in precipitation of the drug and should be avoided. Because of possible microbial contamination during dilution, it is advisable to use the admixture prepared with 5% Dextrose Injection, USP, within 24 hours if refrigerated (2° to 8°C, 36° to 46°F). In the case of admixtures prepared with 5% Dextrose Injection, USP, or Sodium Chloride Injection, USP, the solutions should be used within 6 hours if kept at room temperature (15° to 30°C, 59° to 86°F).

Other drugs should not be added to the infusion solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

Each mL of CAMPTOSAR Injection contains 20 mg irinotecan (on the basis of the trihydrate salt); 45 mg sorbitol; and 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid.

CAMPTOSAR Injection is available in single-dose amber glass vials in the following package sizes:

2 mL NDC 0009-7529-02
5 mL NDC 0009-7529-01

This is packaged in a backing/plastic blister to protect against inadvertent breakage and leakage. The vial should be inspected for damage and visible signs of leaks before removing the backing/plastic blister. If damaged, incinerate the unopened package.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. It is recommended that the vial (and backing/plastic blister) should remain in the carton until the time of use.

℞ only

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for handling parenteral antineoplastics. JAMA 1985; 253(11): 1590-2.
3. National Study Commission on Cytotoxic Exposure. Recommendations for handling cytotoxic agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
4. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. Med J Australia 1983;1:426-8.
5. Jones RB, et. al. Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. CA-A Cancer J for Clinicians, 1983; Sept./Oct., 258-63.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on handling cytotoxic and hazardous drugs. Am J Hosp Pharm 1990; 47:1033-49.
7. OSHA work-practice guidelines for personnel dealing with cytotoxic (antineoplastic) drugs. Am J Hosp Pharm 1986;43:1193-1204.

Camptosar
brand of irinotecan hydrochloride injection

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