



Pharmacia & Upjohn

**Irinotecan Hydrochloride
(CPT-11, CAMPTOSAR®)**

**ONCOLOGIC DRUGS ADVISORY COMMITTEE
BROCHURE**

March 16, 2000

**NDA #20-571, Supplement #9
(First-Line Therapy of Colorectal Cancer)**

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EXECUTIVE SUMMARY

Developmental History of Single-Agent Irinotecan as Second-Line Therapy of Metastatic Colorectal Cancer

Irinotecan hydrochloride injection (CPT-11, CAMPTOSAR® injection) is an antineoplastic agent of the topoisomerase I inhibitor class. Irinotecan was originally developed in Japan by the Yakult Honsha Company and the Daiichi Pharmaceutical Company. Licensing rights for clinical development and commercialization in the United States (US), Canada, Australia, New Zealand, and Latin America were granted to Pharmacia & Upjohn (P&U), whereas similar rights in Europe, Asia, and Africa were granted to Rhône-Poulenc Rorer (now Aventis).

Irinotecan is registered in many countries of the world for the treatment of patients with metastatic colorectal cancer after failure of standard first-line treatment with 5-fluorouracil (5-FU)-based chemotherapy. In particular, it was first approved in the US, Canada, Australia, New Zealand and Latin America on the basis of 3 P&U-sponsored, phase II, open-label, single-arm, uncontrolled studies in which the primary endpoint was tumor response [Dietz 1995a-c]. These trials demonstrated that irinotecan consistently induced objective tumor responses in the second-line setting. These data were supported by results from Japanese and French phase II trials, in which similar antitumor activity was observed [Shimada 1993, Bugat 1994, Blanc 1996]. Based on this collective experience, conditional marketing authorization in the US was granted under Food and Drug Administration (FDA) regulations designed to accelerate approval of new and promising drugs for serious or life-threatening illnesses. The initial New Drug Application (NDA) was approved in 1996.

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]. Both of these trials demonstrated a survival advantage for patients treated with irinotecan, directly confirming the benefit of irinotecan as second-line therapy for patients with metastatic colorectal cancer. Based on these studies – the results of which were provided by Aventis to P&U through a data-sharing agreement – P&U obtained full FDA approval for irinotecan as second-line therapy for patients with metastatic colorectal cancer in 1998.

Development of Irinotecan in Combination with 5-Fluorouracil/Leucovorin as First-Line Therapy of Metastatic Colorectal Cancer

Rationale and Phase I Development

Irinotecan's novel mechanism of action and second-line antitumor activity in 5-FU-refractory colorectal cancer logically lead to its development as a component of first-line therapy of metastatic disease. To this end, irinotecan was combined with existing first-line agents – 5-FU and the 5-FU-modulator, leucovorin (LV). Pilot dose-finding and pharmacokinetics studies of irinotecan/5-FU/LV were performed in order to determine appropriate dosing regimens [Saltz 1996, Mery-Mignard 1999, Vanhoefer 1999]. These trials established safe starting doses for phase III trials and documented that irinotecan pharmacokinetics were not altered by coadministration of 5-FU/LV.

Pivotal Study Designs

Based on the information derived from these pilot studies, 2 pivotal, phase III, randomized, controlled, multicenter, multinational, clinical trials were designed 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. One of these studies (Study M/6475/0038, hereafter described as 0038) was sponsored by P&U and compared combination irinotecan/bolus 5-FU/LV therapy (Saltz regimen) with a standard bolus regimen of 5-FU/LV alone (Mayo Clinic regimen) in patients with previously untreated colorectal cancer [Miller 1999]; an irinotecan-alone treatment arm was included to document the efficacy and safety associated with the first-line use of single-agent irinotecan. The second study (Study RP 64174 A-V-303, hereafter described as V303) was sponsored by Aventis and evaluated two different methods (de Gramont regimen or AIO regimen*) of administering infusional 5-FU/LV, with or without irinotecan [Gruia 1999].

Patient Demographics and Efficacy Results

Important patient characteristics and major efficacy results are shown in Table 1.

Table 1. Overview of Phase III Study Results

	Study 0038			Study V303	
	Irinotecan 5-FU/LV N=231	5-FU/LV N=226	Irinotecan N=226	Irinotecan 5-FU/LV N=198	5-FU/LV N=187
Patient Demographics*					
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 Initial Diagnosis to Randomization (months, range)	1.9 (0-161)	1.7 (0-203)	1.8 (.1-185)	4.5 (0-88)	2.7 (0-104)
Prior Adjuvant 5-FU Therapy (%)					
No	89	91	90	74	77
Yes	11	9	10	26	23
Efficacy Results					
Median TTP (months)	7.0	4.3	4.2	6.7	4.4
	(p = 0.004)†			(p < 0.001)†	
Median TTF (months)	5.5	3.7	3.2	5.3	3.8
	(p = 0.001)†			(p = 0.001)†	
Confirmed Response Rate (%)	39	21	18	35	22
	(p<0.0001)‡			(p<0.005)‡	
Median Survival (months)	14.8	12.6	12.0	17.4	14.1
	(p = 0.042)†			(p = 0.032)†	

*Data not available for some patients who were randomized but not treated, † Log-rank test, ‡ Chi-square test

Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin, TTF = time to treatment failure, TTP = time to tumor progression

* Association of Medical Oncology of the German Cancer Society

With a minimum follow-up of 19 months, both studies demonstrated that the combination of irinotecan/5-FU/LV therapy resulted in highly significant improvements in time to tumor progression (TTP), time to treatment failure (TTF) and objective tumor response rates when compared with 5-FU/LV alone. These tumor control benefits were accompanied by significant survival advantages in both trials. Survival benefit was observed with first-line irinotecan combination treatment even though the majority of patients in the 5-FU/LV control arms of these trials eventually received second-line therapy.

Safety Results

Although the incidence of grade 3 diarrhea in both studies was greater with irinotecan-based combination treatment, rates of grade 4 diarrhea were similar (<8%) when comparing irinotecan/5-FU/LV-treated with 5-FU/LV-treated patients. In Study 0038, grade 4 neutropenia, neutropenic fever, and grade 3/4 mucositis were observed less often with weekly irinotecan/5-FU/LV than with Mayo Clinic 5-FU/LV. Treatment-related death was rare (<1.5%) in all study arms.

Quality of Life Results

The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was used in both studies. In the primary analyses of the mean scores over time, no differences in any of the subscales were observed among treatment arms in either of the studies.

Conclusions

The results of these 2 large, randomized, phase III studies reproducibly document that the combination of irinotecan with 5-FU/LV benefits patients with metastatic colorectal cancer by significantly improving tumor shrinkage, prolonging tumor control, and lengthening survival. These trials also demonstrate that combination irinotecan-based first-line chemotherapy can be given safely, extending life without detriment to quality of life.

Based on the consistently positive benefits documented in these trials, P&U is seeking approval of irinotecan as a component of first-line therapy for patients with metastatic carcinoma of the colon or rectum.

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ABBREVIATIONS AND DEFINITION OF TERMS

5-FU	5-Fluorouracil
AIO	Association of Medical Oncology of the German Cancer Society
ANOVA	Analysis of variance
CEA	Carcinoembryonic antigen
CI	Confidence interval
CTC	Common Toxicity Criteria
EORTC QLQ C-30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C-30
FDA	Food and Drug Administration
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LV	Leucovorin
NCI	National Cancer Institute
NDA	New drug application
P&U	Pharmacia & Upjohn
SD	Standard deviation
SN-38	Active metabolite of irinotecan
sNDA	Supplemental new drug application
TTF	Time to treatment failure
TTP	Time to tumor progression
UNL	Upper normal limit
US	United States
WBC	White blood count

1 BACKGROUND INFORMATION

1.1 Epidemiology and Existing Therapy of Colorectal Cancer

Colorectal cancer is a leading cause of cancer morbidity and mortality with about 300,000 new cases and 200,000 deaths in developed countries each year [Boyle 1998, Midgley 1998]. About 50-60% of patients are cured by surgery alone. However, approximately 20-25% of patients have metastatic disease at diagnosis and the remainder eventually develop metastatic disease.

Available since the late 1950s, the antimetabolite 5-fluorouracil (5-FU) has, until recently, been the only chemotherapeutic option for the treatment of colorectal cancer. 5-FU is a fluorinated pyrimidine that inhibits the function of thymidylate synthase, an enzyme necessary for the production of the thymidine nucleotides required for DNA synthesis. 5-FU is customarily administered with the biomodulating agent, leucovorin (LV), which acts to facilitate affinity with thymidylate synthase, thereby improving 5-FU efficacy [Grem 1996]. It has been established that such cotreatment increases antitumor activity; in a meta-analysis of 9 trials in which a total of 1,381 patients were randomized to receive first-line treatment for metastatic disease with either 5-FU/LV or 5-FU, the combination therapy produced a response rate of 23%, whereas single-agent 5-FU therapy produced an 11% response rate [Advanced Colorectal Cancer Meta-analysis Project 1992]. However, median survival was not altered, remaining less than 12 months despite the addition of LV. It has also been suggested that protracted infusions of 5-FU may offer greater antitumor activity; meta-analysis of this strategy in 1219 patients indicated response rates of 22% with infusional therapy versus 14% with bolus treatment, but median survival again remained at 12 months [Meta-analysis Group in Cancer 1998]. These analyses, which amalgamate years of research, document the limits of 5-FU's potential for controlling tumor growth or improving survival.

When distilled into practice, the "Mayo Clinic" bolus administration regimen of intensive-course 5-FU/low-dose LV has been established as one of the most commonly used first-line therapies for metastatic colorectal cancer in North America [Buroker 1994]. In Europe, administration of LV in conjunction with infusional 5-FU has often been employed based on randomized studies suggesting tumor control benefits. Among the most accepted methods of administration have been the "de Gramont" regimen, involving administration of infusional 5-FU/LV over 2 days every 2 weeks [de Gramont 1997], and a regimen developed by the Association of Medical Oncology of the German Cancer Society (AIO) employing weekly administration of LV with a 24-hour infusion of 5-FU [Weh 1988, Köhne 1998]. Toxicities with 5-FU-based therapy have varied depending upon the schedule of therapy, the method of administration, and the doses of 5-FU and LV, but have included potentially severe diarrhea, mucositis, palmar-plantar erythrodysesthesias (hand-foot syndrome), nausea, vomiting, neutropenia, and neutropenic fever [Buroker 1994, Leichman 1995, Jäger 1996, Meta-analysis Group in Cancer, 1998]

1.2 Irinotecan

1.2.1 Mechanism of Action and Metabolism

Irinotecan is a camptothecin that offers a completely different mechanism of action from that of 5-FU in the therapy of colorectal cancer. Irinotecan functions as a potent inhibitor of topoisomerase I, a nuclear enzyme that plays a critical role in DNA replication and transcription [Pommier 1994]. The enzyme functions normally to cause transient breaks in a single strand of DNA that release the torsional strain caused by synthesis of a new strand of DNA or RNA around the double helix. The camptothecins target this topoisomerase I-DNA complex, known as the "cleavable complex." Once bound to the cleavable complex, the camptothecins stabilize the complex and inhibit reannealing of the parent DNA. Collision of replication forks with the stabilized complex during cell division leads to double-stranded DNA breaks and tumor cell death.

Irinotecan is a prodrug that is metabolized by carboxylesterases in human liver, tumors, and other tissues to the more active lipophilic metabolite, SN-38 [Tsuji 1992]. SN-38 is approximately 1,000 times more potent than irinotecan as an inhibitor of topoisomerase I and is thought to be primarily responsible for irinotecan cytotoxicity [Kawato 1991, Kawato 1995, Matsumoto 1995]. Both irinotecan and SN-38 are primarily cleared via hepatic metabolism and biliary excretion [Schaaf 1998, Slatter 1998].

1.2.2 Efficacy in Metastatic Colorectal Cancer

Irinotecan has demonstrated first-line, single-agent clinical activity in patients with colorectal cancer [Shimada 1993, Bugat 1994, Dietz 1995d, Dietz 1995e]. In the collective results from 2 US phase II studies in which 72 patients with no prior therapy received weekly treatment with irinotecan, outcomes were of generally similar magnitude to those observed with 5-FU/LV [Dietz 1995d, Dietz 1995e]. The confirmed response rate was 29.2%, median time-to-tumor progression (TTP) was 4.2 months, and median survival was 11.4 months. A phase II study involving every-3-week irinotecan treatment in 81 European patients with no prior therapy for metastatic colorectal cancer documented a 19.8% confirmed response rate [Bugat 1994]. Median TTP in these patients was 4.9 months, and median survival was reported to be 14.7 months.

The importance of irinotecan's distinct mechanism of action was clinically validated in the second-line therapy of metastatic colorectal cancer. Irinotecan has been shown to have consistent phase II second-line antitumor activity in patients with 5-FU-refractory disease [Shimada 1993, Dietz 1995a-c, Blanc 1996, Pazdur 1997, Von Hoff 1997, Rothenberg 1998]. This activity has translated into improved survival for patients; 2 randomized, multicenter, phase III trials comparing single-agent irinotecan versus best supportive care [Jacques 1997a], or versus infusional 5-FU/LV therapy [Jacques 1997b] have documented that irinotecan offers a second-line survival advantage to patients after failure of initial 5-FU-based treatment.

1.2.3 Safety Profile

Virtually all studies of irinotecan have reported neutropenia and/or delayed diarrhea (diarrhea generally occurring more than 8 hours after irinotecan administration) as the dose-limiting

toxicities [Shimada 1993, Bugat 1994, Dietz 1995a-e, Blanc 1996, Saltz 1996, Von Hoff 1997, Pazdur 1997, Rothenberg 1998, Mery-Mignard 1999, Gruia 1999, Miller 1999, Vanhoefer 1999]. The frequency of neutropenic fever has been low (usually 3-8%). Clinically significant thrombocytopenia or severe anemia is uncommon. Occurrences of ileus and/or colitis (sometimes with gastrointestinal bleeding) have been observed, but have been rare [Arkhipov 1999].

Patients may have transient cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping and diarrhea (early diarrhea) [Gandia 1993, Bugat 1994, Abigeres 1995, Petit 1997, Miller 1998a]. If they occur, cholinergic symptoms manifest during or shortly after drug infusion and are most commonly mild or moderate in severity.

Other adverse events have included nausea/vomiting, anorexia, delayed abdominal cramping, alopecia, and asthenia [Shimada 1993, Bugat 1994, Dietz 1995a-e, Blanc 1996, Saltz 1996, Von Hoff 1997, Pazdur 1997, Rothenberg 1998, Mery-Mignard 1999, Gruia 1999, Miller 1999, Vanhoefer 1999]. Elevations in serum creatinine have sometimes occurred in association with dehydration as a consequence of diarrhea or severe vomiting [Dietz 1995a-e], or due to occasional tumor lysis syndrome [Persons 1998]. Elevations in hepatic enzymes have been noted, but almost all of these patients have had progressive liver involvement with tumor and a relationship to irinotecan has not clearly been established [Dietz 1995a-e, Mery-Mignard 1999, Vanhoefer 1999].

Based on this toxicity profile, recommendations for supportive care include immediate initiation of loperamide therapy for delayed diarrhea [Abigeres 1994], IV or subcutaneous atropine as prophylaxis or therapy of cholinergic symptoms [Miller 1998a], and antiemetics for prevention of nausea and vomiting [Gruia 1999, Miller 1999, Saltz 1996, Mery-Mignard 1999, Vanhoefer 1999]. Consistent with American Society of Clinical Oncology guidelines [American Society of Clinical Oncology 1994], routine prophylactic use of a colony-stimulating factor is not advised, given the low rate of neutropenic fever generally associated with irinotecan use.

2 PHASE I CLINICAL TRIALS OF IRINOTECAN/5-FU/LV

Irinotecan's novel mechanism of action and its activity in patients with 5-FU-resistant colorectal cancer provided clear rationale for combining irinotecan with 5-FU/LV to improve and prolong tumor control in patients with this disease. Based on these considerations and with attention to the safety profiles of irinotecan and 5-FU/LV, phase I dose-escalation studies were conducted in order to develop regimens for testing in phase III studies.

In the US, P&U conducted a phase I, dose-escalation and pharmacokinetic study in order to develop an irinotecan/5-FU/LV weekly bolus combination regimen (Study 0007)[Saltz 1996]. The recommended regimen from this trial was subsequently employed in the experimental arm of P&U's pivotal phase III trial, Study 0038 [Miller 1999].

In Europe, Aventis sponsored 2 phase I trials to develop irinotecan/5-FU/LV infusional regimens. One of these studies was a phase I, dose-escalation and pharmacokinetic trial of irinotecan with the every-2-week de Gramont 5-FU/LV (Study F106)[Mery-Mignard 1999]. The other involved a dose-escalation of irinotecan with the weekly AIO variation of 5-FU/LV (G101)[Vanhoefler 1999]; pharmacokinetic assessments were not performed in this latter study. Both of the combination regimens developed in these pilot studies were employed in the experimental arm of Aventis's pivotal phase III trial, Study V303 [Gruia 1999].

The clinical results of these phase I studies repeatedly documented that irinotecan can be safely combined with 5-FU and LV. The starting doses achieved in these trials are close to those associated with proved efficacy in single-agent irinotecan trials or studies with 5-FU/LV alone [Weh 1988, Shimada 1993, Dietz 1995a-e, Jäger 1996, de Gramont 1997, Pazdur 1997, Von Hoff 1997, Köhne 1998, Rothenberg 1998] and therapy could be given repeatedly over multiple cycles. No unexpected toxicities were observed. Independent of dose or schedule, clinically meaningful alterations in irinotecan and SN-38 pharmacokinetic parameters were not observed when irinotecan was administered concomitantly with 5-FU/LV. The influence of irinotecan on the pharmacokinetics of 5-FU was not evaluated in the pilot pharmacokinetic studies. However, other clinical trials have indicated that irinotecan does not substantially alter 5-FU pharmacokinetics [Yoshida 1990, Sasaki 1994, Bastian 1998].

3 PHASE III PIVOTAL TRIALS

3.1 Study Methods

3.1.1 Study Design

Study 0038 [Miller 1999] and Study V303 [Gruia 1999] were large, phase III, randomized, controlled, parallel-group, open-label, multicenter, multinational clinical trials evaluating the first-line therapy of patients with metastatic colorectal cancer. In both trials the outcomes in patients randomized to receive combination therapy with irinotecan/5-FU/LV regimens were compared with those in patients randomized to receive regimens containing only 5-FU/LV. In Study 0038 an irinotecan-alone treatment arm was included to document the efficacy and safety associated with the first-line use of single-agent irinotecan in a large multicenter trial.

3.1.2 Entry Criteria

Inclusion and exclusion criteria were generally similar in both trials; adult patients with a histologic diagnosis of metastatic colorectal cancer; measurable tumor lesions; a performance status of 0, 1, or 2; and adequate organ function could be enrolled. In neither study could patients have received prior chemotherapy for metastatic disease. Patients who had received adjuvant 5-FU-based therapy were eligible if this prior treatment had been completed >12 months (Study 0038) or > 6 months (Study V303) before entry into the study. In Study 0038, patients must not have been treated previously with radiotherapy to the abdomen or pelvis, whereas such prior treatment was allowed in Study V303.

3.1.3 Randomization Procedure

In Study 0038, patients were randomized centrally with stratification based on 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). In Study V303, patients were randomized within study center.

3.1.4 Treatment Administration

In Study 0038, patients were allocated to receive 1 of 3 regimens:

Table 2. Treatment Regimens in Study 0038

Arm (Regimen)	Drugs*	Starting Doses	Cycle Schedule
A	Irinotecan	125 mg/m ² IV over 90 minutes	Weekly for 4 weeks every 6 weeks
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 every 6 weeks
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) every 4 weeks

*For each regimen, agents are listed in the order in which administered.

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

In Study V303, patients were allocated to receive 1 of the following treatment regimens:

Table 3. Treatment Regimens in 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 every 7 weeks
	A2 (de Gramont)	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 every 2 weeks 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 every 7 weeks
	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 every 2 weeks

*For each regimen, agents are listed in the order in which administered.

Abbreviations: AIO = Association of Medical Oncology of the German Cancer Society, 5-FU = 5-fluorouracil, IV = intravenous, LV = leucovorin

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

In both trials, patients were to receive repeated cycles of treatment until the occurrence of tumor progression, unacceptable toxicity, or withdrawal of patient consent. After the initial treatment, doses in all arms of each of the studies could be adjusted using specific dose modification rules to accommodate individual patient tolerance of treatment. 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 \leq 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 a 20% reduction in doses was specified. In both trials, patients receiving the irinotecan/5-FU/LV regimen who experienced severe mucositis or hand-foot syndrome were to have only the 5-FU dose adjusted.

3.1.5 Supportive Care

Supportive care in both studies was to include atropine for the treatment of cholinergic symptoms, loperamide for the treatment of late diarrhea and antiemetic agents for the prophylactic treatment of nausea and/or vomiting. The prophylactic use of colony-stimulating factors was not advocated; however, the use of granulocyte colony-stimulating factor was permitted for prolonged neutropenia or for the treatment of infectious complications during neutropenic episodes. In Study V303, 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.

3.1.6 Endpoints

The major clinical efficacy endpoints were similar in the 2 trials; both studies evaluated confirmed objective tumor response rates, time to tumor progression (TTP), time to treatment failure (TTF), and survival. The primary endpoint in Study 0038 was TTP. In Study V303, the primary endpoint was tumor response rate. The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was used in both studies. Serial changes in weight and performance status were analyzed in both trials. Safety was characterized in terms of the incidence of adverse events, laboratory abnormalities, discontinuations due to adverse events, and treatment-related deaths.

3.1.7 Type and Timing of Assessments

In Study 0038, tumor measurements were to be obtained every 6 weeks until Week 24, and then every 12 weeks until tumor progression was observed. In Study V303 tumor measurements were to be obtained after each cycle (every 6-7 weeks), and at the end of study treatment. Objective tumor responses were to be confirmed at least 4 weeks after the first documentation of response. Quality of life, performance status, body weight and serum chemistries were to be assessed at the beginning of each treatment cycle. Assessments of adverse events were to be obtained at each visit and complete blood counts were to be performed weekly during chemotherapy. Following completion of study drug therapy, information regarding post-study treatments for colorectal cancer and survival was also collected.

3.1.8 Statistical Analyses

For both studies, major time-to-event endpoints (eg, TTP, TTF, time to response, duration of response, and survival) were analyzed by Kaplan-Meier curves and unstratified log-rank tests. Response rates were compared using chi-square tests. The influence of stratification factors and other baseline characteristics on confirmed objective tumor response rates were assessed using multiple regression modeling. Similarly TTP and survival were assessed using Cox proportional hazard regression modeling.

At the start of each cycle of therapy, patients completed the EORTC QLQ-C30, which consists 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). Using standard EORTC procedures, the answers from the 30 questions are converted into 15 subscales that are scored from 0 to 100. The global health status subscale within the EORTC instrument is derived from 2 questions about the patient’s sense of general well being in the past week. In addition to the global health status subscale, there are 5 functional (ie, cognitive, emotional, social, physical, role) and 9 symptom (ie, fatigue, appetite loss, pain assessment, insomnia, constipation, dyspnea, nausea/vomiting, diarrhea, financial impact) subscales. In Study 0038, global health status, role functioning, and pain subscales were selected as primary quality of life endpoints in the statistical comparison. In Study V303, the global health status subscale was considered primary for the quality of life analysis.

Quality of life was assessed using ANOVA for repeated measurements. In Study 0038, mean best and worst scores and changes in these scores from baseline were tabulated. Life-table methods and log-rank testing were employed in testing the influence of treatment on declines in weight and performance status over time.

Relative dose intensity was calculated as the ratio of actual dose intensity ($\text{mg}/\text{m}^2/\text{day}$) to the planned dose intensity ($\text{mg}/\text{m}^2/\text{day}$) for each patient's entire course of treatment. Safety was summarized by treatment arm with categorization of the incidence of adverse and laboratory events according to each patient's worst severity grade. The severity of adverse events and laboratory changes were graded according to the US National Cancer Institute (NCI) Common Toxicity Criteria (CTC), Version 1.0.

3.1.9 Sample Size Calculations

Based on a review of past experience with first-line 5-FU-based chemotherapy for colorectal cancer [Buroker 1994, Leichman 1995], median TTP in the 5-FU/LV arm of Study 0038 was judged to be 5 months. A 40% improvement, corresponding to a benefit ratio of 1.4 (hazard ratio of 0.714), in median TTP from 5 to 7 months in patients receiving the combination of irinotecan/5-FU/LV (Arm B), as compared with those receiving 5-FU/LV (Arm C), was considered to be clinically meaningful. Employing a 2-tailed unstratified log-rank test with significance level of 0.05, 324 events across these 2 treatment arms were required to detect this magnitude of difference with a power of 0.85. The significance level of 0.05 was used in the analyses since it was decided a priori that the only statistical hypotheses of the study were based on the comparison of these 2 arms. The statistical analysis was to be performed once the required number of events had occurred. Assuming that the analysis would be conducted when approximately 80% of the patients on treatment had developed progressive disease, 203 patients were to be enrolled per treatment arm. The sample size was set at 220 patients per treatment arm under the assumption that up to 10% of the patients might drop out before objective evidence of tumor progression had been obtained.

In the sample size calculation for Study V303, the response rate was assumed to be equal to 35% for 5-FU/LV (Arm B), whereas the response rate for the combination irinotecan/5-FU/LV (Arm A) was assumed to be equal to 50%. Using a 2-tailed chi-square test with a significance level of 0.05, the number of patients needed to show a significant difference in response rate between 5-FU/LV (35%) and irinotecan/5-FU/LV (50%) with a power of 0.80 was estimated to be 169 patients per treatment arm or a total of 338 evaluable patients.

This sample size was also estimated to be sufficient to show a significant difference between the 2 treatment arms in the secondary endpoint of TTP, assuming that TTP would be 6 months in the 5-FU/LV arm (Arm B) and 9 months in the irinotecan/5-FU/LV arm (Arm A). Assuming an accrual time of 6 months and a minimum follow-up time of 9 months and using a 2-tailed log-rank test with a significance level of 0.05, the minimum number of patients needed per treatment arm was estimated to be 143 with a power of 0.80. Since it was anticipated that 5% of the enrolled patients would be lost to follow-up, it was estimated that a minimum of 151 patients would need to be enrolled in each treatment arm (302 patients overall) to adequately evaluate TTP.

3.2 Results

3.2.1 Patient Enrollment

Study 0038 was conducted by P&U at 71 sites, including 49 sites in the US, 11 sites in Canada, 8 sites in Australia, and 3 sites in New Zealand. Study V303 was conducted by Aventis at 83 sites in Europe, Israel and South Africa.

Study 0038 enrolled and randomized a total of 683 patients between May of 1996 and May of 1998. Patient survival data were collected and updated for an additional 19 months after closure of accrual, with a final data cut-off date for survival of December 1999. Of those randomized, 231 patients were allocated to receive irinotecan/5-FU/LV (Arm B), 226 patients were allocated to receive 5-FU/LV (Arm C), and 226 were allocated to receive irinotecan alone (Arm A); these patients constituted the intent-to-treat population that was planned as the primary focus of efficacy analyses in this trial. Four of the 231 patients randomized to the irinotecan/5-FU/LV arm, 8 of the 226 patients randomized to the 5-FU/LV arm, and 4 of the 226 patients randomized to the irinotecan-alone arm never received treatment. Two of the patients who were to receive irinotecan/5-FU/LV, 1 of the patients who was to receive 5-FU/LV, and 1 of the patients who was to receive irinotecan alone received treatment with a regimen other than that to which they had been randomized. Thus, the as-treated population used in the dose intensity, safety, and quality of life analyses included 225 patients who actually were given irinotecan/5-FU/LV (Arm B), 219 patients were received 5-FU/LV (Arm C), and 223 patients who were treated with irinotecan alone (Arm A).

Study V303 enrolled and randomized a total of 387 patients between May of 1997 and February 1998. In this trial, patient survival data were collected and updated for an additional 20 months after closure of accrual, with a final data cut-off date for survival of October 1999. Of those randomized, 199 patients were allocated to receive irinotecan/5-FU/LV and 188 patients were allocated to receive 5-FU/LV. One of the 199 patients randomized to the irinotecan/5-FU/LV arm and 1 of the 188 patients randomized to the 5-FU/LV arm never received treatment. The remaining population of 198 patients in the irinotecan/5-FU/LV group (53 in Group A1 and 145 in Group A2) and 187 patients in the 5-FU/LV group (44 in Group B1 and 143 in Group B2) constituted the full-analysis population that was planned as the primary focus of efficacy and quality of life analyses in this trial. One of the patients who was to receive 5-FU/LV alone actually received irinotecan/5-FU/LV. Thus, the as-treated population used in the dose intensity and safety analyses included 199 patients who actually were given irinotecan/5-FU/LV (54 in Group A1 and 145 in Group A2) and 186 patients who received 5-FU/LV (43 in Group B1 and 143 in Group B2). The fact that approximately three-quarters of the full-analysis patients enrolled in the trial were randomized to receive the A2/B2 (145/143 patients) schedule of treatment (de Gramont regimens) and about one-quarter received the A1/B1 (53/44 patients) schedule of therapy (AIO regimens) was due to the distribution of study sites participating in Study V303.

3.2.2 Patient Characteristics

Baseline patient characteristics are presented in Table 4.

Table 4. Baseline Patient Characteristics in 2 Phase III Studies

Patient Characteristic	Study 0038			Study V303	
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV	5-FU/LV
	Arm B N = 231	Arm C N = 226	Arm A N = 226	Arm A N = 198	Arm B N = 187
Age					
Median (years, range)	62 (25-85)	61 (19-85)	61 (30-87)	62 (27-75)	59 (24-75)
Gender					
Male	151 (65.4%)	123 (54.4%)	145 (64.2%)	132 (66.7%)	99 (52.9%)
Female	79 (34.2%)	101 (44.7%)	80 (35.4%)	66 (33.3%)	88 (47.1%)
Not available*	1 (0.4%)	2 (0.9%)	1 (0.4%)	-- --	-- --
Performance Status					
0	89 (38.5%)	93 (41.2%)	104 (46.0%)	102 (51.5%)	96 (51.3%)
1	106 (45.9%)	102 (45.1%)	103 (45.6%)	83 (41.9%)	77 (41.2%)
2	35 (15.2%)	29 (12.8%)	18 (8.0%)	13 (6.6%)	14 (7.5%)
Not available*	1 (0.4%)	2 (0.9%)	1 (0.4%)	-- --	-- --
Site of Primary Tumor					
Colon	188 (81.4%)	192 (85.0%)	189 (83.6%)	108 (54.5%)	121 (64.8%)
Rectum	38 (16.5%)	31 (13.7%)	33 (14.6%)	90 (45.5%)	66 (35.5%)
Not available*	5 (2.2%)	3 (1.3%)	4 (1.8%)	-- --	-- --
Number of Involved Organ Sites					
1	147 (63.6%)	149 (65.9%)	140 (61.9%)	123 (62.1%)	117 (62.6%)
2	59 (25.5%)	52 (23.0%)	64 (28.3%)	46 (23.2%)	53 (28.3%)
>2	24 (10.4%)	23 (10.2%)	21 (9.3%)	29 (14.6%)	17 (9.1%)
Not available*	1 (0.4%)	2 (0.9%)	1 (0.4%)	-- --	-- --
Time from Initial Diagnosis to Randomization					
Median (months, range)	1.9 (.1-161)	1.7 (.1-203)	1.8 (.1-185)	4.5 (.1-88)	2.7 (0-104)
Time From Diagnosis of Metastatic Disease to Randomization					
Median (months, range)	1.1 (0-43)	1.3 (0-49.9)	1.2 (.1-30)	1.4 (0-67)	1.6 (0-92)
Prior Adjuvant 5-FU					
No	206 (89.2%)	208 (92.0%)	203 (89.8%)	147 (74.2%)	143 (76.4%)
Yes	25 (10.8%)	18 (8.0%)	23 (10.2%)	51 (25.8%)	44 (23.5%)
Prior Radiotherapy					
Any Radiotherapy	7 (3.0%)	5 (2.2%)	3 (1.3%)	40 (20.2%)	29 (15.5%)
Pelvis/Abdomen	4 (1.7%)	2 (0.9%)	3 (1.3%)	-- --	-- --
Other Sites	3 (1.3%)	3 (1.3%)	0 (0.0%)	-- --	-- --
Baseline Laboratory Abnormalities					
CEA ≥100 ng/mL	89/224 (39.7%)	82/213 (38.5%)	81/219 (37.0%)	67/192 (34.9%)	59/182 (32.4%)
Hemoglobin <11 g/dL	58/227 (25.6%)	55/217 (25.3%)	57/221 (25.8%)	32/198 (16.2%)	40/187 (21.4%)
WBC ≥8 x 10 ³ /mm ³	119/227 (52.4%)	115/217 (53.0%)	113/221 (51.1%)	93/197 (47.2%)	71/187 (38.0%)
LDH >UNL	126/210 (60.0%)	112/201 (55.7%)	104/195 (53.3%)	68/158 (43.0%)	70/156 (44.9%)
Total Bilirubin >UNL	15/226 (6.6%)	9/218 (4.1%)	22/220 (10.0%)	13/196 (6.6%)	13/186 (7.0%)

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

Abbreviations: CEA = carcinoembryonic antigen, 5-FU = 5-fluorouracil, LDH = lactate dehydrogenase, LV = leucovorin, UNL = upper normal limit, WBC = white blood count

3.2.2.1 Demographics

The median ages were generally similar across all treatment groups in both trials, ranging from 59 to 62 years. There were no restrictions on enrollment of older patients in Study 0038, resulting in a maximum patient age (87 years) that was higher than that (75 years)

enforced in Study V303. Across the arms of the studies, there was a predominance of males, with men accounting variably for 52% to 67% of those enrolled. A significantly greater proportions of males were enrolled to the treatment arms than to the control arms (Study 0038, 65.4% [irinotecan/5-FU/LV] versus 54.4% [5-FU/LV], Chi-square $p=0.019$; Study V303, 66.7% [irinotecan/5-FU/LV] versus 52.9% [5-FU/LV], Chi-square $p=0.006$). While there was some variability in baseline performance status across studies, the populations were generally divided similarly between patients with performance status 0 and those with performance status 1-2. However, the proportion of patients with a performance status of 2 in the irinotecan/5-FU/LV treatment and 5-FU/LV control groups of Study 0038 (approximately 13-15%) was almost double the proportion of patients in either arm of Study V303 (approximately 7-8%) with performance status 2.

3.2.2.2 Disease Characteristics

Colonic primary tumors predominated in both studies, as might be expected given the epidemiology of the disease. The proportion of patients with rectal tumors in Study 0038 (approximately 15%) was notably lower than that (35-45%) in Study V303, perhaps because patients with prior pelvic irradiation were excluded from Study 0038, but not from Study V303. The number of involved organ sites was very similar across the studies. The median time from initial diagnosis to randomization was less than 2 months in Study 0038 and was somewhat longer in Study V303; these findings indicate that most patients participating in these trials already had metastatic disease at the time of primary diagnosis of colorectal cancer. In general, patients in both studies were randomized to treatment within 2 months of the diagnosis of metastatic disease.

3.2.2.3 Prior Therapy

Because most patients had metastatic disease at initial diagnosis, only a minority of patients (approximately 10% in Study 0038 and 25% in Study V303) had received prior adjuvant 5-FU treatment. A history of previous radiation therapy was rare in Study 0038 because patients were to have been excluded if they had undergone prior irradiation to an abdominal or pelvic site. Since this was not an exclusion criterion in Study V303, greater proportions of patients were enrolled who had received radiotherapy. Information regarding the specific sites of irradiation, particularly data indicating the frequency of prior abdominal or pelvic radiotherapy, was not provided for the V303 trial.

3.2.2.4 Baseline Laboratory Abnormalities

Several baseline laboratory values were specifically assessed based on past reports suggesting that these factors may be prognostic for outcome in patients with colorectal cancer [Kemeny 1989, Rougier 1995, Jacques 1997a, Jacques 1997b, Miller 1998b]. While there were few differences between the studies in baseline CEA or total bilirubin levels, it is notable that the proportion of patients with depressed hemoglobin, elevated WBC or abnormal serum LDH was higher in Study 0038 than in Study V303, perhaps indicating a greater tumor burden or degree of tumor-related organ dysfunction among the patients enrolled to the 0038 trial.

3.2.3 Treatment Administration

3.2.3.1 On-Study Treatment

Assessment of administration of irinotecan and 5-FU, taking into account the influences of both dose modifications and delays in treatment, is most readily observed when examining the relative dose intensities achieved in each arm of the trials. Table 5 shows results for relative dose intensity for Studies 0038 and V303.

Table 5. Median Relative Dose Intensity* in 2 Phase III Studies

Agent	Study 0038			Study V303			
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV		5-FU/LV	
	Arm B N = 225	Arm C N = 219	Arm A N = 223	Arm A N = 198		Arm B N = 187	
				A1 N=54	A2 N=145	B1 N=43	B2 N=143
Irinotecan	0.72	--	0.75	0.82	0.93	--	--
5-FU	0.71	0.86	--	0.81	0.92	0.90	0.96

*Ratio of actual dose intensity (mg/m²/day) to the planned dose intensity (mg/m²/day) for each patient's entire course of treatment

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

As might be expected, 5-FU median relative dose intensities were lower in the irinotecan-containing combination arms than in the control arms of both trials. It is also apparent that the median relative dose intensities of both irinotecan and 5-FU administered in Study 0038 were somewhat lower than those in Study V303. The reason for this difference between studies may relate to the fact that the V303 protocol did not specify dose reductions of more than 20%, whereas the Study 0038 protocol provided guidelines for as many as 3 successive decrements of 20%. In addition, in Study 0038, doses were to be reduced by 20% for grade 2 or 3 toxicities and by 40% for grade 4 toxicities. In contrast, either grade 3 or 4 toxicity called for only a 20% dose reduction in Study V303.

In Study 0038, assessment of the influence of each drug in the combination on the relative dose intensity was possible because of the inclusion of an irinotecan-only treatment group (Arm A). The median relative irinotecan dose intensities in Study 0038 were similar in Arms A (0.75) and B (0.72). This suggests that the presence of 5-FU in Arm B caused relatively little further reduction in irinotecan dose intensity in the Study 0038 combination regimen. Conversely, the median 5-FU relative dose intensity (0.71) in Arm B was lower than that in Arm C (0.86), suggesting a greater influence of irinotecan on 5-FU delivered dose intensity in the combination regimen. However, this apparently greater effect of irinotecan on 5-FU delivery may be influenced by the differences in schedules between the regimens and from the weekly dose reductions permitted in the Arm B regimen. In Study V303, where the compared 5-FU schedules (A1 versus B1 and A2 versus B2) were the same, only modest reductions in median 5-FU relative dose intensity were observed when irinotecan was added to 5-FU.

3.2.3.2 Post-Study Treatment

When information regarding post-study anticancer therapy was tabulated for Study 0038, these data documented that 53.8% (106/197) of irinotecan/5-FU/LV-treated patients (Arm B)

received post-study therapy as contrasted with 70.2% (139/198) of 5-FU/LV-treated patients (Arm C). Among the Arm-C patients, 55.6% (110/198) received post-study irinotecan-based therapy, specifically.

In Study V303, 41.4% (82/198) of the patients randomized to irinotecan/5-FU/LV (Arm A) were given post-study therapy while 59.4% (111/187) of the patients randomized to first-line 5-FU/LV (Arm B) received post-study treatment. Among the Arm-B patients, 31.0% (58/187) received post-study, second-line irinotecan therapy. The proportion of patients receiving second-line oxaliplatin-containing treatment was similar in the 2 treatment groups in V303; such treatment was administered to 15.5% (31/198) of those randomized to irinotecan/5-FU/LV versus 12.2% (23/187) randomized to 5-FU/LV.

3.2.4 Efficacy

Efficacy data from the pivotal studies are presented in Table 6, focusing on the major efficacy endpoints of tumor control, ie, TTP, TTF, confirmed objective tumor response rates, and survival.

Table 6. Efficacy Results from 2 Phase III Studies

Efficacy Endpoint	Study 0038			Study V303			
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV		5-FU/LV	
	Arm B N = 231	Arm C N = 226	Arm A N = 226	Arm A N = 198		Arm B N = 187	
				A1 N=53	A2 N=145	B1 N=44	B2 N=143
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)*			
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 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)*			

* Unstratified log-rank test

† Chi-square test

§ Confirmed ≥ 4-6 weeks after first evidence of objective response

Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin, TTF = time to treatment failure, TTP = time to tumor progression

3.2.4.1 TTP and TTF

Remarkable consistency across the studies was observed when examining the efficacy outcome measures. In both trials, TTP and TTF were significantly improved ($p \leq 0.004$ for each comparison) with combination irinotecan/5-FU/LV therapy than with 5-FU/LV alone.

When considering the median overall values for these endpoints in Study V303, the results correspond closely to those observed in Study 0038. The TTP and TTF results in Study V303 were strongly influenced by the outcomes in patients randomized to A2 versus B2; in the A1 versus B1 comparison, the small number of patients may have contributed to the lack of apparent differences.

3.2.4.2 Objective Tumor Response Rate and Response Duration

In both trials, confirmed objective response rates were significantly improved ($p < 0.005$) with irinotecan-based combination therapy over those observed with 5-FU/LV alone. In Study 0038, the odds ratio in favor of irinotecan/5-FU/LV was 2.48 (95% CI, 1.64-3.73) while that in Study V303 was 1.90 (95% CI, 1.21-2.99). When considering the 2 different regimens tested in Study V303 separately, the odds ratio for improvement was similar for the A1 versus B1 comparison (odds ratio 1.97 [95% CI, 0.82-4.73]) as for the A2 versus B2 comparison (odds ratio 1.86 [95% CI, 1.10-3.17]). This difference was statistically significant for A2 versus B2 ($p = 0.021$) but not for A1 versus B1, most likely due to the small sample size of the A1/B1 subpopulations. The median duration of confirmed objective tumor response from the time of randomization among the subset of responding patients was consistently in the range of 9 months for all treatment arms. In every subgroup – including those with poor performance status, extensive metastatic disease, prior adjuvant therapy, or abnormal baseline laboratory values – the response rate with irinotecan/5-FU/LV was always approximately double that with 5-FU/LV alone.

3.2.4.3 Survival

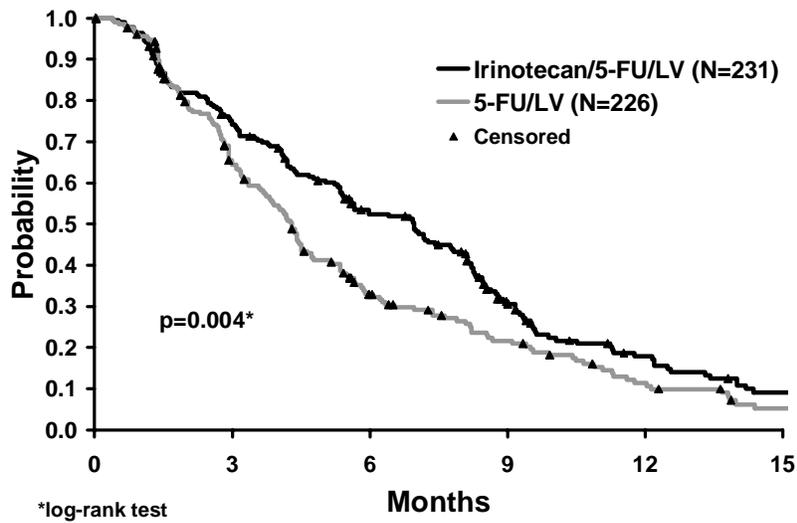
Critically important was the observation that survival was improved when irinotecan was given together with 5-FU/LV. Comparison of the survival with irinotecan/5-FU/LV versus that with 5-FU/LV in Study 0038 showed a significant difference ($p = 0.042$, unstratified log-rank test); patients randomized to irinotecan/5-FU/LV had a 19% reduction in the risk of death relative to those allocated to 5-FU/LV alone (hazard ratio 0.81, 95% CI=0.65-0.99). Similarly, survival was significantly prolonged with irinotecan/5-FU/LV therapy in Study V303 ($p = 0.032$, unstratified log-rank test); there was a 23% reduction in the risk of death with irinotecan/5-FU/LV relative to only 5-FU/LV (hazard ratio 0.77, 95% CI=0.60-0.98). The survival improvement was highly significant in the comparison of the larger subpopulations of A2 versus B2 ($p = 0.01$). The curves for the smaller A1/B1 subpopulations were not meaningfully different ($p = 0.84$).

3.2.4.4 Kaplan-Meier Curves

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 from 2 Phase III Studies

Study 0038



Study V303

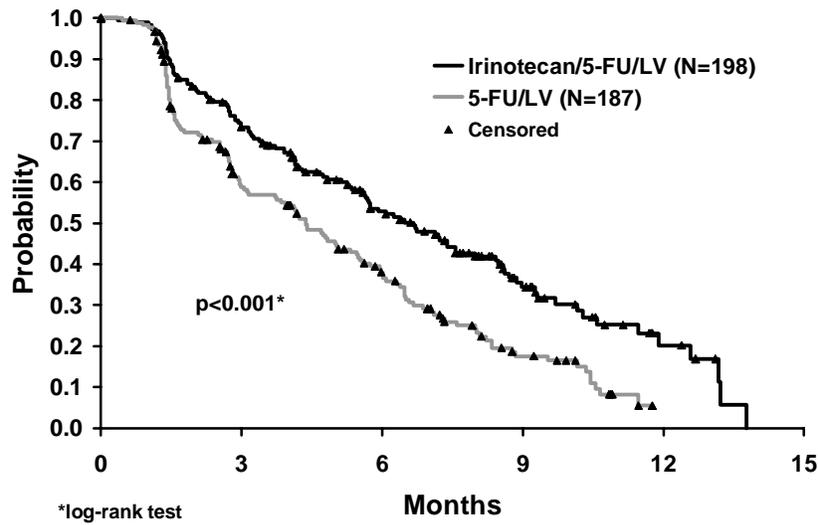
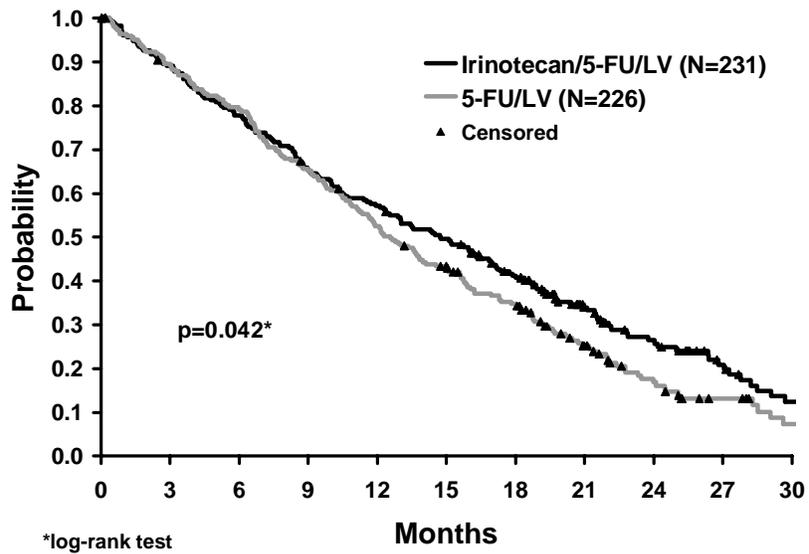
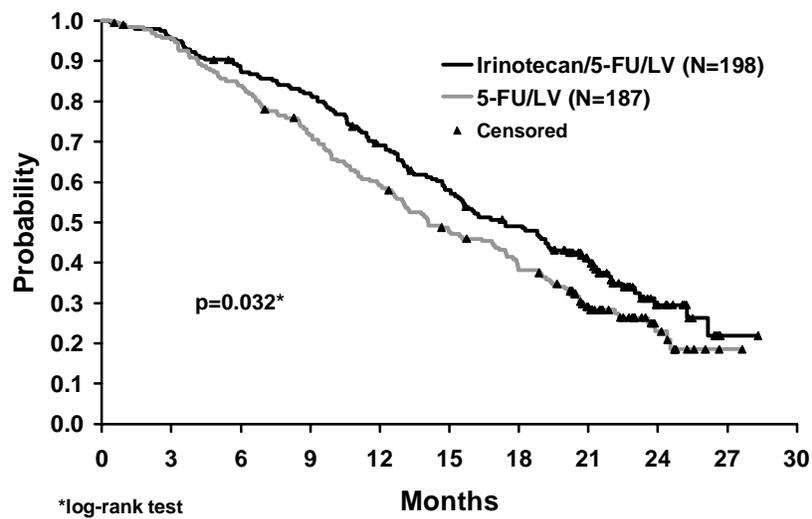


Figure 2. Survival -- Kaplan-Meier Estimates from 2 Phase III Studies

Study 0038



Study V303



3.2.4.5 Study 0038 Arm A Results

While the statistical hypotheses in Study 0038 focused on the comparison of the irinotecan/5-FU/LV experimental therapy (Arm B) with the standard 5-FU/LV regimen (Arm C), the results with irinotecan alone (Arm A) are also noteworthy. Inspection of the response rates and median time-to-event endpoints indicates general similarity of outcomes between Arms A and C.

3.2.5 Cox Regression Modeling

In a preplanned analysis in Study 0038, Cox regression techniques were used to evaluate the effect of treatment (irinotecan/5-FU/LV [Arm B] versus 5-FU/LV [Arm C]) on outcome in the context of the stratification factors and the other predefined patient baseline characteristics. Baseline patient characteristics in this analysis included the 4 stratification factors (age, performance status, time from initial diagnosis, and prior adjuvant therapy) and other baseline factors of potential prognostic significance (gender, ethnic origin, site of primary tumor, time from diagnosis of metastatic disease, number of involved organ sites, liver involvement, serum CEA, hemoglobin, WBC, serum LDH, and serum total bilirubin).

As shown in Table 7, among the most consistently predictive factors for improved TTP and survival were normal LDH and good performance status along with lesser number of organ sites involved and normal bilirubin. Higher hemoglobin and normal WBC were also significantly predictive of better TTP and survival, respectively. Unexpectedly, older age also appeared to be prognostic for improved TTP. Treatment with combination irinotecan/5-FU/LV remained a significant independent predictor of enhanced TTP and survival when significant baseline patient characteristics were taken into account. In this adjusted analysis, treatment with irinotecan/5-FU/LV was associated with a 36% lower risk of tumor progression and a 20% lower risk of death relative to treatment with 5-FU/LV.

Table 7. Cox Regression Results from Study 0038

Factor		TTP			Survival		
		Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p
Serum LDH	≤UNL vs >UNL	0.60	0.47-0.76	0.0001	0.47	0.37-0.60	0.0001
Performance Status	0 vs ≥1	0.74	0.59-0.93	0.0088	0.57	0.45-0.71	0.0001
Number of Organ Sites	1 vs ≥2 sites	0.63	0.50-0.80	0.0001	0.67	0.54-0.84	0.0004
Bilirubin	≤UNL vs >UNL	0.56	0.35-0.89	0.0132	0.55	0.35-0.86	0.0051
WBC	<8 vs ≥8 x10 ³ /mm ³				0.64	0.51-0.80	0.0001
Hemoglobin	≥11 vs <11 g/dL	0.74	0.58-0.95	0.0157			
Age	≥65 vs <65 years	0.78	0.63-0.98	0.0315			
Treatment	Irinotecan/5-FU/LV vs 5-FU/LV	0.64	0.51-0.79	0.0001	0.80	0.64-0.99	0.0372

Abbreviations: 5-FU = 5-fluorouracil, CI = confidence interval, LV = leucovorin, UNL = upper limit of normal, TTP = time to tumor progression, WBC = white blood count

In order to assess the prognostic strength of the Cox regression model derived from Study 0038, the effect of treatment was assessed in Study V303 in the context of the same baseline patient factors. The results of this analysis are described in Table 8. As in Study 0038, predictive factors for improved TTP and survival included normal baseline serum LDH and

fewer involved organs; better performance status was also significantly associated with longer survival. In Study V303, a longer time from diagnosis of metastatic disease to randomization was predictive for better outcomes in terms of both TTP and survival. In this adjusted analysis, treatment with irinotecan/5-FU/LV was associated with a 42% lower risk of tumor progression and a 23% lower risk of death relative to treatment with 5-FU/LV.

Table 8. Cox Regression Results from Study V303

Factor		TTP			Survival		
		Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p
Serum LDH	≤UNL vs >UNL	0.61	0.46-0.80	0.0012	0.55	0.42-0.72	0.0001
Performance Status	0 vs ≥1				0.52	0.41-0.67	0.0001
Mo from Met Diagnosis	≥1 vs <1	0.62	0.48-0.80	0.0003	0.63	0.49-0.82	0.0005
Number of Organ Sites	1 vs ≥2 sites	0.71	0.55-0.91	0.0070	0.73	0.57-0.94	0.0127
Treatment	Irinotecan/5-FU/LV vs 5-FU/LV	0.58	0.45-0.75	0.0001	0.77	0.61-0.98	0.0365

Abbreviations: 5-FU = 5-fluorouracil, CI = confidence interval, LV = leucovorin, Met = metastatic, Mo = months, UNL = upper limit of normal, TTP = time to tumor progression

3.2.6 Safety

Table 9 provides safety data from the 2 pivotal studies. In both studies, approximately 23% of patients treated with the combination irinotecan/5-FU/LV regimens experienced grade 3/4 diarrhea compared with approximately 10-14% of patients receiving 5-FU/LV alone. This difference was primarily in the incidence of grade 3 diarrhea; grade 4 diarrhea – largely defined by the need for hospitalization for supportive care – was comparably infrequent in the treatment and control arms of the 2 trials (eg, 7.6% in Arm B and 7.3% in Arm C of Study 0038). In Study V303, the increase in grade 3 diarrhea seemed most apparent in the comparison of the A1/B1 (AIO) regimens.

As expected, grade 3/4 vomiting was somewhat more common with irinotecan-based therapy, but occurred in <10% of patients in any of the combination arms. Grade 4 vomiting – usually that which requires hospitalization for supportive care – was observed in <6% of patients in any arm of the 2 trials.

Of note, grade 3/4 mucositis was quite infrequent with irinotecan-based therapy, occurring in <4% of patients receiving combination therapies. By contrast, the schedule of 5-FU/LV used in the control arm of Study 0038, and commonly employed as first-line therapy in North America, was associated with a much higher frequency of severe, grade 3/4 mucositis (16.9%).

While both grade 3 and 4 neutropenia frequencies are reported in Table 9, only the occurrence of grade 4 neutropenia is usually associated with clinical consequences. Of interest, the frequency of grade 4 neutropenia with combination therapy (24.0%) in Study 0038 was essentially half that observed in patients receiving 5-FU/LV in the control group (42.5%); also notable was that proportionately fewer patients experienced neutropenic fever when contrasting irinotecan/5-FU/LV (7.1%) with 5-FU/LV (14.6%). In Study V303, where schedules of chemotherapy administration were similar, grade 4 neutropenia was more frequently seen when irinotecan was added to 5-FU/LV (A1, 5.8%; A2, 9.8%) than with 5-FU/LV alone (B1, 2.4%; B2, 0.7%). The incidence of neutropenic fever was also higher in the irinotecan/5-FU/LV arm (5.0%) than in the 5-FU/LV arm (1.1%); however, these rates of

neutropenic complication are quite low when contrasted with many other chemotherapy regimens.

Discontinuations due to adverse events were acceptably low across all arms of both studies. The incidence of treatment-related death was <1.5% in all treatment groups.

Table 9. Adverse Events in 2 Phase III Studies

Adverse Event	Study 0038			Study V303			
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV		5-FU/LV	
	Arm B N = 225	Arm C N = 219	Arm A N = 223	Arm A N = 199		Arm B N = 186	
				A1 N=54	A2 N=145	B1 N=43	B2 N=143
Diarrhea (%)							
Grade 3/4	22.7	13.2	31.0	22.6		10.8	
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	
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	
Grade 3	2.2	14.6	1.8	0.0	4.1	2.3	2.8
Grade 4	0.0	2.3	0.4	0.0	0.0	0.0	0.0
Neutropenia (%)							
Grade 3/4	53.8	66.7	31.4	41.8		10.9	
Grade 3	29.8	23.7	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
Neutropenic Complications (%)							
Neutropenic Fever	7.1	14.6	5.8	5.0		1.1	
Neutropenic Infection	1.8	0.0	2.2	2.0		0.0	
Discontinuations Due to Adverse Events and Drug-related Deaths (%)							
Discontinuations	7.6	6.4	11.7	9.0		2.7	
Drug-Related Deaths	0.9	1.4	0.9	0.5		0.0	

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

3.2.7 Quality of Life and Additional Measures of Clinical Benefit

Quality of life (assessed using the EORTC QLQ C-30) and additional measures of clinical benefit (changes in weight and performance status) were also assessed in patients participating in both Study 0038 and Study V303.

As specified in the 0038 protocol, the subscales of global health status, role functioning, and pain symptoms were to be emphasized. A repeated-measurement ANOVA in Study 0038 indicated that the estimated pattern of change from baseline did not result in significant differences between the treatment arms in these subscales. Most patients participating in the study did not have clinically significant reductions in weight or performance status during treatment; as a consequence, the power to detect differences between treatment arms for these endpoints was low and no significant results were noted.

Similar findings were apparent in Study V303. The repeated-measurement ANOVA showed that the evolution of the different scales during treatment was very similar in both groups. In V303, the time to definitive performance status deterioration was significantly longer in patients treated with irinotecan/5-FU/LV than in those treated with 5-FU/LV alone (median 11.2 months versus 9.9 months; log-rank $p = 0.046$).

3.3 Discussion

These 2 phase III, randomized, multicenter, multinational, well-controlled studies compared the efficacy and safety of new combinations of irinotecan/5-FU/LV to that of standard regimens of 5-FU/LV as first-line therapy of metastatic colorectal cancer. The two studies were complimentary in that they assessed the efficacy and safety of the combination of irinotecan with two common methods of 5-FU/LV administration (bolus and infusional therapy). Study 0038 evaluated a new combination of irinotecan/bolus 5-FU/LV to that of the Mayo Clinic regimen of bolus 5-FU/LV that has been a North American standard. Study V303 symmetrically determined the therapeutic ratio associated with adding irinotecan to 2 infusional 5-FU/LV regimens that are widely used in Europe; only a single variable, that of adding irinotecan, was altered in the comparison of the 2 groups.

A common feature to both studies was a lower relative dose intensity of 5-FU in the treatment arms than in the control arms. This design characteristic provides reassurance that the incremental benefits in efficacy observed in the studies can be attributed specifically to the irinotecan and not to improved delivery of 5-FU.

The efficacy results of both studies were remarkably consistent and show that combination therapy provides patients with a significant delay in tumor progression while reducing tumor size. In Studies 0038 and V303, respectively, the endpoint of TTP was significantly improved with combination treatment (medians, 7.0 and 6.7 months) over 5-FU/LV alone (medians, 4.3 and 4.4 months). TTF was also consistently and significantly enhanced by combination treatment versus 5-FU/LV in Study 0038 and in V303 (medians, 5.4 and 5.3 months versus 3.7 and 3.8 months, respectively). In addition, the confirmed objective tumor response rates with the irinotecan/5-FU/LV combination arms (39.4% and 34.8%) were 1.5-2 times those in the 5-FU/LV control arms (20.8% and 21.9%); these results were highly statistically significant in both trials. When response rates and time to tumor progression data were examined across demographic and disease-related subgroups, irinotecan-based combination therapy universally improved tumor control relative to 5-FU/LV. These findings indicate that all patients have a chance to benefit from improved tumor control with irinotecan/5-FU/LV.

The most critical finding of the studies is that first-line irinotecan/5-FU/LV combination treatment provided a significant survival advantage even though most control patients received second-line therapy after on-study failure of 5-FU/LV. These findings indicate that early combination irinotecan/5-FU/LV treatment has advantages relative to a sequence of first-line 5-FU followed by second-line irinotecan. Such a finding is consistent with the results of a landmark study conducted in Scandinavia in which asymptomatic patients with colorectal cancer were randomized to receive immediate 5-FU-based chemotherapy or to receive delayed 5-FU-containing treatment once symptoms developed [Nordic Gastrointestinal Tumor Adjuvant Therapy Group 1992]. Early treatment in the Nordic trial

was also associated with a significant improvement in survival as compared to the delayed-therapy approach.

Cox regression modeling, assessing treatment effect adjusted for significant prognostic factors, reinforced the primary analyses of both Studies 0038 and V303, confirming that combination therapy with irinotecan/5-FU/LV improves time to tumor progression and survival. These data indicated irinotecan/5-FU/LV treatment resulted in an approximate 40% reduction in the relative risk of tumor progression and a 20% decrease in the relative risk of death.

In Study 0038, the irinotecan-alone treatment arm was included to document the efficacy and safety associated with the first-line use of single-agent irinotecan in a large multicenter study. While statistical testing was not performed to evaluate the combination regimen versus the irinotecan-alone arm, the results of the irinotecan-alone arm bolster confidence in the results of the study. Most notable is the consistency of the response rate and median TTP, TTF, response, and survival values with irinotecan alone relative to these same values with 5-FU/LV alone.

Gastrointestinal toxicity was more common with combination treatment. However, it is notable that rates of grade 4 diarrhea – usually that associated with hospitalization for hydration – were similarly infrequent with either the irinotecan/5-FU/LV or 5-FU/LV treatment arms. Moreover, rates of grade 4 neutropenia, neutropenic fever, and mucositis were actually less often observed with weekly irinotecan/5-FU/LV than with Mayo Clinic bolus 5-FU/LV alone in Study 0038. As described in past comparisons of weekly versus monthly 5-FU/LV therapy [Buroker 1994, Leichman 1995], this reduced toxicity with combination therapy is most likely due to the differences in 5-FU/LV scheduling between the experimental and control arms. The addition of irinotecan to 5-FU/LV in Study V303 increased the likelihood of Grade 3 diarrhea; this effect was more prominent with the A1/B1 (AIO) regimen than with the A2/B2 (de Gramont) regimen. Other clinically relevant Grade 3 and 4 events, eg, vomiting, mucositis, and neutropenic fever, were infrequent with either V303 regimen. Discontinuations due to adverse events were acceptably low. Treatment-related death was rare in all study arms. The safety findings were supported by the results in the analysis of quality of life. These data document that combining irinotecan with 5-FU/LV provides improved tumor control and survival without resulting in significant decrements in quality of life relative to 5-FU/LV alone.

3.4 Benefit/Risk Assessment

The benefits and the risks of the irinotecan/5-FU/LV combination compared to 5-FU/LV alone are summarized in Table 10 (for Study 0038) and Table 11 (for Study V303). Both of these summaries clearly demonstrate that the first-line benefits of irinotecan-based combination therapy outweigh the risks.

Table 10. Study 0038 Overall Benefit/Risk Assessment

Parameters	Irinotecan 5-FU/LV	5-FU/LV	Benefit of Irinotecan/ 5-FU/LV with Respect to 5-FU/LV
Efficacy			
Confirmed Tumor Response Rate (%)	39.4	20.8	Positive ^a
Median TTP (months)	7.0	4.3	Positive ^b
Median TTF (months)	5.4	3.7	Positive ^c
Median Survival (months)	14.8	12.6	Positive ^d
Safety			
Grade 4 Neutropenia (%)	24.0	42.5	Positive
Neutropenic Fever (%)	7.1	14.6	Positive
Grade 3/4 Mucositis (%)	2.2	16.9	Positive
Grade 3/4 Vomiting (%)	9.7	4.1	Negative
Grade 3 Diarrhea (%)	15.1	5.9	Negative
Grade 4 Diarrhea (%)	7.6	7.3	Similar
Discontinuations Due to Adverse Events (%)	7.6	6.4	Similar
Drug-Related Deaths (%)	0.9	1.4	Similar
Quality of Life			
All 15 Subscales			Similar

^a p<0.0001 (Chi-square), ^b p=0.004 (log-rank), ^c p=0.001 (log-rank), ^d p=0.042 (log-rank)

Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin, TTF = time to treatment failure, TTP = time to tumor progression

Table 11. Study V303 Overall Benefit/Risk Assessment

Parameters	Irinotecan 5-FU/LV	5-FU/LV	Benefit of Irinotecan/ 5-FU/LV with Respect to 5-FU/LV
Efficacy			
Confirmed Tumor Response Rate (%)	34.8	21.9	Positive ^a
Median TTP (months)	6.7	4.4	Positive ^b
Median TTF (months)	5.3	3.8	Positive ^c
Median Survival (months)	17.4	14.1	Positive ^d
Safety			
Grade 4 Neutropenia (%)	8.7	1.1	Negative
Neutropenic Fever (%)	5.0	1.1	Negative
Grade 3/4 Mucositis (%)	3.0	2.7	Similar
Grade 3/4 Vomiting (%)	5.5	3.2	Similar
Grade 3 Diarrhea (%)	17.1	6.5	Negative
Grade 4 Diarrhea (%)	5.5	4.3	Similar
Discontinuations Due to Adverse Events (%)	9.0	2.7	Negative
Drug-Related Deaths (%)	0.5	0.0	Similar
Quality of Life			
All 15 subscales			Similar

^a p=0.005 (Chi-square), ^b p<0.001 (log-rank), ^c p=0.001 (log-rank), ^d p=0.032 (log-rank)

Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin, TTF = time to treatment failure, TTP = time to tumor progression

4 OVERALL CONCLUSIONS

Attempts to improving outcome in patients with metastatic colorectal cancer with the limited tools of 5-FU and LV has been the source of decades of frustration and disappointment. Irinotecan has now repeatedly proved the ability to break the barrier to improved survival, first as single-agent second-line therapy, and now as a component of first-line combination treatment. The pivotal phase III studies contained in this submission are the first trials to document that the combination of a new agent with 5-FU/LV can safely benefit patients with metastatic colorectal cancer by inducing tumor shrinkage and extending tumor control, and that these outcomes are associated with significantly prolonged life without an impairment of quality of life. The results of these adequate and well-controlled studies convincingly demonstrate that first-line irinotecan-containing combination treatment sets a new standard and should be recommended for approval in the management of this life-threatening disease.

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