Phase II studies of fluorouracil (5-FU) administered by protracted intravenous infusion have suggested an improved response rate and decreased toxicity profile when compared with 5-FU given by bolus injection in patients with metastatic colorectal cancer. Additional studies have suggested further enhancement of infusion 5-FU activity when it is combined with low-dose weekly cisplatin administration. Purpose: This phase III study in adults with metastatic colorectal cancer was planned as a comparison of objective response rates, toxicity, and survival in patients receiving bolus versus protracted-infusion 5-FU with or without cisplatin. Methods: Four hundred ninety-seven previously untreated patients with advanced, measurable metastatic colorectal cancer were randomly assigned to receive treatment A (bolus 5-FU at 500 mg/m² for 5 days followed in 2 weeks by weekly bolus 5-FU at 600 mg/m²), treatment B (bolus 5-FU at 500 mg/m² for 5 days followed in 2 weeks by weekly bolus 5-FU at 600 mg/m²), plus weekly cisplatin at 20 mg/m²), treatment C (5-FU at 300 mg/m² per day by continuous infusion), or treatment D (5-FU at 300 mg/m² per day by continuous infusion plus weekly cisplatin at 20 mg/m²). All drugs were administered intravenously. Enrollment in the trial occurred from August 1987 through December 1990, and follow-up was through September 1995. The Kaplan–Meier method was used to estimate overall and disease-free survival, and Cox regression models were used to assess the effects of patient characteristics on survival. All P values resulted from two-sided tests. Results: Objective tumor response was observed in 28 (18%) of 153 patients receiving treatment A, in 45 (28%) of 159 patients receiving treatment C (C versus A; P = .045), and in 47 (31%) of 153 patients receiving treatment D (D versus A; P = .016). Because of excessive toxicity, treatment B was discontinued after only 12 patients had begun treatment. Median time to disease progression was 5.1 months for patients in arm A compared with 6.2 and 6.5 months for patients in arms C and D, respectively (C versus A, P = .007; D versus A, P = .017). Patterns of toxic effects differed substantially among the treatment arms. Forty-five percent of the patients receiving bolus 5-FU alone (A) experienced grade 3-4 leukopenia, with two sepsis-related deaths. Hand-foot syndrome and mucositis were the major treatment-limiting toxic effects for patients in the two treatment arms involving infusion. Despite the improvement in response rates and time to disease progression with infusion 5-FU with or without cisplatin (C and D, respectively) (P = .003), the overall survival for the three groups (A, C, and D) was similar (P = .307). This may have been due in part to a longer median survival time of 10.4 months for patients in arm A, compared with an anticipated survival of 7 months. Conclusion: 5-FU given as a continuous infusion produced a higher objective response rate, a modest prolongation in time to disease progression, and less life-threatening myelosuppression in patients than bolus 5-FU. Concomitant treatment with low-dose cisplatin caused added toxicity and complexity of treatment and did not provide a major clinical benefit. No statistically significant survival differences were observed among the three treatment groups. [J Natl Cancer Inst 1996;88:668-74]
Materials and Methods

The objective of this study (EST 2286) was to compare the response rate, response duration, toxicity, time to disease progression, and overall survival in patients treated with bolus 5-FU compared with those treated with continuous-infusion 5-FU with or without cisplatin. The study began in August 1987 and initially used a factorial design to address these comparisons. Patients were randomly assigned to receive either bolus 5-FU alone, bolus 5-FU with cisplatin, infusion 5-FU alone, or infusion 5-FU plus cisplatin. Under this design, half of the patients were to receive bolus 5-FU and half were to receive continuous-infusion 5-FU. Furthermore, half of the patients were to have their 5-FU dose combined with cisplatin and half were not. Assuming no interactive effects between the two factors, a factorial design thus allows the assessment of the effects of the two different factors on outcome, and uses only slightly more patients than would be needed for a single-factor study. Survival was planned to be the primary end point of the study, although disease-free survival and tumor response were also to be analyzed. Initially, it was planned that 350 patients would enter the study. Assuming accrual over approximately 4 years, this number was estimated to provide 87% power to detect an improvement in median survival from 7 to 10 months (i.e., an increase of 3 months) between two arms (assuming a one-response, 450 patients would provide 84% power to detect an improvement in median survival). In terms of tumor response, 350 patients would provide 87% power to detect an improvement from 7 to 10.5 months (a 50% improvement). The final planned sample size was estimated to provide 87% power to detect an improvement in median survival from 7 to 10 months (i.e., an increase of 3 months) between two arms (assuming a one-response, 450 patients would provide 84% power to detect an improvement in median survival). In terms of tumor response, 350 patients would provide 87% power to detect an improvement from 7 to 10.5 months (a 50% improvement).

Therapy Evaluation Program of the National Cancer Institute, the Food and Drug Administration, and the Human Investigational Review Board at each institution.

After 12 patients were treated with bolus 5-FU plus cisplatin, however, this treatment arm was discontinued because of an unacceptable high rate of myelosuppression. The trial continued thereafter as a three-arm randomized trial. These changes in the design had a major impact on the planned sample size for the study. Because the study no longer had a factorial design, it was no longer valid, for example, to assess the effects of bolus versus continuous-infusion 5-FU by combining arms with or without cisplatin. Instead, each arm in the revised trial required sufficient patient numbers to provide power for comparisons with either of the other two arms. Several other changes were implemented at the time of the study redesign. First, Bonferroni adjustments were planned so that each test was to be performed at level .025 to ensure an overall significance level of .05. Second, a sequential design was implemented to allow for early stopping in the case of strong treatment differences. The final planned sample size was a total of 450 patients, or 150 per arm, which would provide 90% power to detect an improvement from 7 to 10.5 months (a 50% improvement in median survival). In terms of tumor response, 450 patients would provide 84% power to detect an improvement in response rates from 20% to 35% between any two arms (assuming a one-sided binomial test at level .025). Four interim analyses were planned after approximately 18, 30, 36, and 42 months, followed by a final analysis at 48 months. Accrual began in August 1987 and was planned to be completed after 36 months, but was not accomplished until December 1990 (i.e., after 40 months). The average accrual was 17 patients per month. Because accrual took longer than the anticipated 36 months, we extended patient follow-up through September 1995 to ensure that the study was adequately powered.

To be eligible for this study, patients had to have previously untreated metastatic adenocarcinoma of the colon or rectum with a pathologically confirmed diagnosis and no hope of surgical resection. The disease had to be measurable in two dimensions on physical examination, computed tomography scan, chest x-ray, or magnetic resonance scan. Malignant hepatomegaly was acceptable if the liver contained biopsy-proven cancer and if the liver edge clearly extended at least 5 cm below the costal margin or the xiphoid process. The patients were required to be at least 18 years of age and to have adequate bone marrow function, defined as a white blood cell count greater than or equal to 4000/mm$^3$ and a platelet count greater than or equal to 100,000/mm$^3$. A bilirubin level less than or equal to 1.5 mg/100 mL, and a serum creatinine level less than or equal to 1.5 mg/100 mL. Performance status was required to be at least 0, 1, or 2, based on ECOG criteria (15), and the patient had to have a life expectancy of at least 3 months. Patients with any prior chemotherapy were ineligible, although they were allowed to have had previous biologic therapy as long as chemotherapy had not been given.

Before randomization, patient eligibility was confirmed by a protocol-specific checklist. Each patient provided written informed consent before being randomly assigned to a treatment arm. The patients were stratified before random assignment by performance status (0 versus 1 or 2) and location of metastases (hepatic versus other sites).

Chemotherapy consisted of treatment arm A (bolus 5-FU at 500 mg/m$^2$ intravenously for 5 days followed in 2 weeks by weekly 5-FU at 600 mg/m$^2$ intravenously), arm B (same as A + cisplatin at 20 mg/m$^2$ per week intravenously immediately before 5-FU and on day 1 of the 5-day 5-FU loading course), arm C (5-FU infusion at 300 mg/m$^2$ per day by continuous infusion), and arm D (same as C + cisplatin at 20 mg/m$^2$ per week intravenously). The dose of infusion 5-FU was permanently decreased by 50 and 100 mg/m$^2$ for grade 2 and 3 nonhematologic toxicity, respectively. The dose of infusion 5-FU was not modified for hematologic toxicity. The doses of bolus 5-FU and cisplatin were temporarily decreased if the WBC count was less than 2500/mm$^3$ and/or the platelet count was less than 75,000/mm$^3$. The dose of bolus 5-FU and cisplatin were permanently decreased if the WBC count was less than 2500/mm$^3$ and/or the platelet count was less than 75,000/mm$^3$. The doses of bolus 5-FU and cisplatin were permanently decreased by 25% and 50% for grade 2 and 3 nonhematologic toxicity, respectively.

The patients were evaluated for response every 8 weeks. Standard ECOG response criteria were used. A CR was defined as the complete disappearance of all clinically detectable malignant disease for at least 4 weeks, with normalization of all scans and x-rays. A PR was defined as at least a 50% decrease in the sum of the products of the longest perpendicular diameters of all indicated lesions for at least 4 weeks. There could be no significant weight loss (>10%) or deterioration of performance status (1 score level). The patients were considered to have had disease progression if any new metastatic lesions developed during therapy, if there was any deterioration in performance status related to cancer, or if there was a more than 25% increase in the area of any malignant lesion greater than 2 cm. Duration of response was measured from the time of documented response to the date of disease progression. Survival was measured from the date of entry in the study. Time to disease progression was defined as the interval from the date of entry in the study to the appearance of any new metastatic lesions or other evidence of objective tumor progression. Confidence intervals for the objective response rate were determined by the exact method (16). Distributions of survival time and time to disease progression were estimated by the Kaplan-Meier method (17). Cox regression models were used to test the effects of patient characteristics on survival and time to disease progression (17). Stratification factors were adjusted for by including them as factors in the Cox models. The logrank test (16) was used for univariate comparisons among treatment groups and other factors with respect to survival and time to disease progression. All reported P-values resulted from two-sided statistical tests.

Results

A total of 497 patients were entered in the study, and all were randomly assigned to a treatment group. Thirteen patients did not receive protocol treatment, two never provided any on-study information, one was lost to follow-up, and four were ineligible. Thus, 477 patients were fully eligible with on-study and follow-up information available. Twelve patients were randomly assigned to receive the bolus 5-FU plus cisplatin arm before it closed. Thus, 465 patients were randomly assigned to receive treatment in one of the three arms that are the main focus of this report, namely, those involving administration of bolus 5-FU, infusion 5-FU, or infusion 5-FU plus cisplatin.

Demographic characteristics were evenly distributed among the different treatment groups. Most patients were male (65%), white (90%), and aged 60 years or older (65%), with metastases to the liver (77%). Almost all of the patients (91%) had good performance status (level 1 or 2), and 56% had experienced no weight loss in the previous 6 months. Curative surgery had been attempted in 48% of the patients, and palliative surgery had been performed in 56% of the patients. Various previous radiotherapy had been administered in 18% of patients.

Toxicity

Four hundred seventy-eight patients had information available regarding tox-
icity. This number included three eligible patients but excluded two eligible patients with missing toxicity information because of early treatment termination. The worst grades of treatment-related toxic effects, coded according to standard ECOG toxicity criteria, are summarized in Table 1.

The excessive toxicity that led to early closure of arm B is clearly apparent from Table 1. Of the 12 patients who received bolus 5-FU plus cisplatin, all experienced at least moderate toxic effects. Severe reactions included fever, diarrhea, and skin and renal toxic effects. Life-threatening toxic effects included hematologic and respiratory toxic effects and infection. The two patients who died on this arm both experienced hematologic toxic effects. The rate of lethal toxicity was quite low (1%) on all three remaining arms (A, C, and D). Arm A (bolus 5-FU alone) had a substantially higher rate of life-threatening toxicity than the two infusion arms. The major toxicity on arm A was hematologic, mainly leukopenia, following the initial 5-day loading course. Grades 3 and 4 hematologic toxic effects were observed in 22% and 24% of the patients on arm A, respectively. In contrast, grades 3 and 4 hematologic toxic effects were observed in only 6% and 1% of the patients on the infusion arms (C and D combined), respectively. The most common nonhematologic toxicity occurred in the skin and mucous membrane. Grade 2 stomatitis requiring treatment interruption was seen in 51 (33%), 56 (35%), and 47 (31%) of the patients in arms A, C, and D, respectively. Grade 3 stomatitis requiring treatment interruption was seen in four (2%), 57 (36%), and 54 (35%) of the patients in arms A, C, and D, respectively. Severe vomiting and diarrhea were more common on arm D (approximately 10%), slightly less so on arm A (approximately 7%), and least common on arm C (approximately 3%). Of the 313 patients with catheters or venous ports, catheter-related problems occurred with the following frequency: thrombosis in 57 (18%) patients, exit-site infection in 44 (14.1%), malposition in 11 (3.5%), occlusion in six (1.9%), sepsis in six (1.9%), fibrin sleeve in six (1.9%), breakage in five (1.6%), and pinch-off with embolus in one (0.3%).

Objectives

Of the 477 eligible patients with follow-up information on all four arms, objective responses were seen in 123 patients, including 17 (4%) CRs and 106 (22%) PRs. Thirty-eight patients were considered unassessable for response, although they are included in the denominator of the reported response rates. The most common reason for unassessability was lack of follow-up scans because of either patient refusal or early treatment termination due to death or toxicity. The rates of unassessability were evenly distributed across treatment arms (excluding the early-terminated arm B). When the unassessable patients were excluded, the CR and PR rates changed to 4% and 24%, respectively.

The overall response rates (CR and PR combined) were 18% (28 of 153 patients), 25% (three of 12), 28% (45 of 159), and 31% (47 of 153) for patients treated on arms A, B, C, and D, respectively. CR rates were 3% (five of 153 patients), 0% (none of 12), 5% (eight of 159), and 3% (five of 153) for patients treated on arms A, B, C, and D, respectively. Patients on arms C and D had significantly better response rates than patients on arm A (P = .045 and P = .016, respectively). These calculations count unassessable patients as nonresponders and include them in the denominator for response rate comparisons. When the unassessable patients are excluded from the analysis, the response rates increase slightly and the associated P values become slightly smaller. As expected, patients with a better performance status (ECOG 0 versus 1 and 2) experienced higher overall response rates (34% versus 20%). Patients with metastatic disease in the peritoneum did particularly poorly (response rate, 20%) as did patients with disease in intra-abdominal lymph nodes. Younger patients (<40 years old) also did very poorly, with no responses observed among the 11 patients in this category.

Survival

The overall median survival time of the 477 eligible patients with follow-up was 12.6 months; 2- and 3-year survival rates of 19% and 6%, respectively, were observed. Table 2 summarizes survival within various patient subgroups. Factors significantly associated with survival included performance status, weight loss, primary tumor site, whether there was adjacent anatomic involvement, degree of differentiation, and location of distant metastases. As expected, patients with a good performance status had a relatively long survival compared with those with a poorer performance status. Patients with weight loss had a shorter survival than those who had not lost weight. Patients who underwent surgical resection of their primary tumor did better than those who did not have surgery. There was also evidence that patients with disease in the rectum or lower colon had a longer survival than patients with disease located in

<table>
<thead>
<tr>
<th>Treatment arm*</th>
<th>No. of patients</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Life-threatening</th>
<th>Lethal</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (bolus 5-FU)</td>
<td>153</td>
<td>3 (2)</td>
<td>9 (6)</td>
<td>51 (33)</td>
<td>49 (32)</td>
<td>39 (25)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>B (bolus 5-FU + DDP)</td>
<td>12</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (25)</td>
<td>4 (33)</td>
<td>3 (25)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>C (CI 5-FU)</td>
<td>159</td>
<td>3 (2)</td>
<td>24 (15)</td>
<td>82 (52)</td>
<td>43 (27)</td>
<td>6 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>D (CI 5-FU + DDP)</td>
<td>154</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td>30 (20)</td>
<td>69 (45)</td>
<td>11 (7)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Total</td>
<td>478</td>
<td>6 (1)</td>
<td>35 (7)</td>
<td>216 (46)</td>
<td>155 (32)</td>
<td>59 (12)</td>
<td>7 (1)</td>
</tr>
</tbody>
</table>

*5-FU = fluorouracil; DDP = cisplatin; CI = continuous infusion.
the right cecum or transverse colon. Time to disease progression and overall survival are shown in Figs. 1 and 2, respectively. The 12 patients on arm B, who were treated with bolus 5-FU and cisplatin, were excluded. Median time to disease progression with bolus 5-FU (arm A) was 5.1 months compared with 6.2 and 6.5 months for patients treated with infusion 5-FU without or with cisplatin (arms C and D), respectively. These differences achieved statistical significance (C versus A, \(P = .007\); D versus A, \(P = .017\)). The median survival time was 10.4 months for patients treated with bolus 5-FU (A) compared with 13.0 months for patients who received continuous-infusion 5-FU alone (C) and 13.0 months for patients who had cisplatin added to continuous-infusion 5-FU (D). However, these differences were not statistically significant (C versus A, \(P = .223\); D versus A, \(P = .586\)). We also compared survival and progression-free survival for the 312 patients who received infusion 5-FU (with or without cisplatin) versus the 153 patients who did not. There was no significant difference with respect to overall survival (\(P = .307\)), but there was a strongly significant difference with respect to progression-free survival (\(P = .003\)).

Multivariate Cox models were used to assess the simultaneous effects of various factors on survival and time to relapse. Factors that retained prognostic significance in the Cox model as predictors for poorer survival included poor performance status, weight loss, presence of residual primary tumor, and metastatic disease located in the lung, liver, abdominal nodes, or peritoneum. Factors that retained prognostic significance as predictors for a shorter time to disease progression included poor performance status and having metastatic disease located in the lung, liver, abdominal nodes, or peritoneum. After adjusting for these factors, treatment with infusion 5-FU (either with or without cisplatin) significantly improved time to disease progression compared with treatment with bolus 5-FU.

### Discussion

5-FU administered in traditional bolus schedules has only modest effect in the treatment of advanced colorectal cancer (1). Following administration, bolus 5-FU is rapidly cleared from the blood and has a very short plasma half-life. Protracted infusion of 5-FU has the theoretic advantage of providing continuous drug exposure (18). In addition, protracted infusion increases both the dose intensity and total cumulative dose of 5-FU compared with bolus administration. The numerous complex intracellular actions of 5-FU when administered by protracted infusion have been previously reviewed and probably involve both DNA-related and RNA-related targets (19).

Lokich et al. (2) showed initially in a phase I study that the drug could be administered for protracted periods with acceptable toxicity, consisting predominantly of stomatitis and hand-foot syndrome. Subsequent phase II studies demonstrated an overall response rate of approximately 36% (range, 15%-39%) (4-12), suggesting that 5-FU may be more effective when administered by protracted infusion. In 1989, the MAOP reported a prospective randomized study comparing bolus and infusion 5-FU in the treatment of advanced colorectal cancer (13). In that study, an increased response rate was seen in patients with infusion therapy. However, there was no difference in overall survival. In addition, a randomized study of bolus versus infusion 5-FU given for 2 weeks on followed by 2 weeks off demonstrated prolonged time to disease progression with infusion treatment but no difference in survival (20). A randomized phase II trial designed as a screening trial evaluating bolus versus infusion 5-FU as well as other 5-FU modulations was completed by the Southwest Oncology Group (21). In contrast to the previously mentioned
trials, it did not show a difference between response rate for bolus versus infusion methods. None of the trials demonstrated a difference in median survival times. The longest survival, however, was seen in the infusion arm, and the trial design was a randomized phase II trial rather than a formal phase III comparison. Our own study, EST 2286, corroborates the findings of the MAOP study, both demonstrating improved objective response rates in patients treated with 5-FU infusion compared with those receiving bolus 5-FU. In EST 2286, however, the response rate with bolus 5-FU was higher than the response rate in the MAOP study, leading to a less significant difference in response between bolus and infusion 5-FU. In both the MAOP study and EST 2286, the CR rate for 5-FU infusion was low, and in all four studies there was no significant difference in survival between bolus and 5-FU infusion schedules.

As described in the “Materials and Methods” section, EST 2286 was designed with high power (90%) to detect a 50% improvement in median survival time. If the control median survival time had been as low as originally anticipated (around 7 months), then a 50% improvement would have corresponded to an improvement of 3.5 months, thus reaching 10.5 months in total. In fact, survival for patients assigned to the control arm in our study was quite good (10.6 months). Hence, even though we saw an improvement of almost 3 months among patients treated with infusion 5-FU, this corresponded to only a 23% improvement in median survival time. Although we might have considered designing the study to detect a smaller difference of approximately 25%-30%, it would have required a much larger study. For example, if in the beginning we had designed the study to have around 80% power to detect a 25% improvement in median survival time, approximately 1300 patients would have been needed. Would you agree that a 25% improvement in median survival time is not a clinically important enough difference for this patient population, especially for a treatment strategy as complex as infusion chemotherapy? Consequently, we felt that such a large study would not have been warranted.

Investigators have noted clinical utility of 5-FU and cisplatin combinations in the treatment of head and neck, esophageal, and other cancers. In 1987, Cantrell et al. (14) reported a substantially improved response rate in patients with colorectal cancer when they were treated with a combination of 5-FU infusion and weekly low-dose cisplatin. In that study, 21 of 30 assessable patients achieved either CR or PR. On the basis of that report, the combination of cisplatin and 5-FU appeared to be substantially superior to 5-FU infusion alone. Enhanced effectiveness with the combination was consistent, with improved benefit seen with the combination in head and neck and esophageal cancers at that time. Consequently, this combination of 5-FU infusion and weekly low-dose cisplatin was also evaluated in EST 2286. Although the objective response rate in EST 2286 was slightly higher in those patients receiving cisplatin compared with those receiving 5-FU infusion alone, it did not achieve statistical significance, and there was no meaningful impact on survival. This is consistent with other later reports of 5-FU and cisplatin combinations in colorectal cancer (22-26).

Our study corroborated the previously observed differences in toxicity between bolus and infusion 5-FU. Severe life-threatening bone marrow suppression with bolus 5-FU (usually following the loading course) occurred in approximately 25% of the patients; there were two treatment-related deaths. In contrast, bone marrow suppression is minimal with 5-
FU infusion schedules. The most frequent side effects from infusion therapy included stomatitis and hand-foot syndrome that could be relatively easily managed with temporary treatment breaks. Bone marrow suppression was not common with infusion schedules. One patient who had a normal WBC count died of catheter-related sepsis.

Continuous-infusion 5-FU improves the response rate over bolus 5-FU with less toxicity and lengthens the time to disease progression. These results are balanced, however, by the lack of significant difference in overall survival and requirement for placement of an indwelling central catheter and the use of an ambulatory pump. Not unexpectedly, there was a relatively high incidence of catheter complications across this multiinstitutional study. Approximately 30% of the patients developed a significant catheter-related problem, adding to the inconvenience and complexity of infusion therapy.

Since protracted-infusion 5-FU improves the response rate, produces a modest improvement in time to disease progression, and produces less life-threatening toxicity, it may be considered as an initial approach in the treatment of advanced colorectal cancer. The economic implications of protracted-infusion regimens are being evaluated prospectively in a randomized phase III intergroup trial. Further benefits of infusion 5-FU therapy have been observed in the adjuvant treatment of rectal cancer, where infusion 5-FU has been shown to be superior to bolus 5-FU when used during pelvic irradiation, with resultant improvement in both disease-free and overall survival (27). The current intergroup rectal adjuvant study is investigating the use of protracted venous infusion 5-FU before, during, and after pelvic radiation compared with standard bolus 5-FU.

Infusion 5-FU may also ultimately be shown to play a role as an adjuvant therapy in colon cancer. Current standard adjuvant therapy in colon cancer uses bolus 5-FU and levamisole therapy that has been relatively ineffective in advanced disease setting (28). In view of the established benefit of 5-FU and levamisole in the adjuvant setting, despite marginal benefit in the advanced disease setting, the use of protracted-infusion 5-FU in the adjuvant setting may result in substantial improvement in response rates and overall curability. A current intergroup study of patients with colon cancer is investigating the benefit of 1 week of adjuvant 5-FU infusion in the perioperative period when added to standard adjuvant bolus 5-FU and oral levamisole. A second intergroup colon cancer adjuvant trial is comparing postsurgical protracted-infusion 5-FU plus levamisole with bolus 5-FU, levamisole, and leucovorin. The results from these ongoing trials will help clarify the role of adjuvant-infusion 5-FU in the management of patients with colorectal cancer.

### References

Notes

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