# Adjuvant Therapy for Colon Cancer

Leonard B. Saltz, MD[a,b]

**KEYWORDS**

• Adjuvant therapy • Colorectal cancer • Disease-free survival
• 5-FluorouracilU

Patients are not at risk of dying from tumor that has been removed; they are at risk of dying from residual microscopic disease not removed at the time of operation. Thus, the goal of an adjuvant treatment, be it chemotherapy, radiation therapy, immunotherapy, or dietary and lifestyle manipulations, is to eradicate any residual, albeit microscopic, metastatic disease that might remain. If the surgeon has truly "gotten it all," then the patient is cured and there is no need or justification for subjecting the patient to any further treatment. It is because of the inability to determine definitively who does and who does not harbor micrometastatic disease that adjuvant therapy, predominantly chemotherapy, is administered to large numbers of patients with resected colon cancer, many of whom may have already been rendered disease-free by their operation.

Clinical stage remains the best prognostic indicator of the risk of what is somewhat inaccurately referred to as recurrence. Thus, stage is the best predictor of whether the patient harbors undetected microscopic stage IV disease. Stage is determined by the depth of tumor penetration into or through the bowel wall and the number of lymph nodes involved with cancer. Present recommendations are for the examination of an absolute minimum of at least 12 lymph nodes to assure accurate resection and staging. Adequate nodal examination reflects a combination of adequate nodal resection on the part of the surgeon, plus adequate nodal inspection on the part of the pathologist.

Stage I disease carries an excellent prognosis, and at present there are no compelling data to support adjuvant chemotherapy for patients with this early-stage disease. Stage II colon cancer also has a relatively good prognosis after operation alone and represents the most complicated and contentious area in decisions regarding the use of adjuvant chemotherapy. Stage III colorectal cancer (CRC) (Tany$N_{1-2}M_0$) represents a group at a higher risk of recurrence, and this population is routinely given adjuvant chemotherapy in the absence of a medical or psychiatric contraindication.

[a] Colorectal Oncology Section, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
[b] Department of Medicine, Weill Medical College of Cornell University, New York, NY 10065, USA
*E-mail address:* saltzl@mskcc.org

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Extensive retrospective data have resulted in the segregation of patients with stage III cancer into 3 subgroups based on T category and N category within stage III (IIIA: T1–2, N1; IIIB: T3–4, N1; IIIC: T0–4, N2).[1] The 5-year observed survival rates for these 3 subcategories were 60%, 42%, and 27%, respectively ($P<.001$), with surgery alone indicating the heterogeneity of stage III cancer and the importance of this subcategorization in anticipating prognosis. Similar differences were calculated after stratification for treatment reporting a 5-year observed survival rate of 71%, 51%, and 33% with surgery plus adjuvant fluoropyrimidine chemotherapy for each subgroup, respectively. The data supporting the use of adjuvant therapy in patients with colon cancer are reviewed in later discussion.

## HISTORICAL DEVELOPMENT OF ADJUVANT THERAPY

Initial adjuvant trials in colon cancer were negative, due in large part to their being extremely undersized (as few as 30–50 patients per arm), based on unrealistically high expectations of the effect of chemotherapy. The first adequately powered study to address the question was the US Intergroup Trial INT-0035.[2] In this trial, patients receiving 1 year of 5-fluorouracil (5-FU), plus the putative immunomodulator levamisole, experienced a 33% risk reduction compared with the surgery-only control group. In retrospect, levamisole has been shown to be an inactive agent; however, the trial was the first to give adequate doses of 5-FU to a large enough patient population to discern an effect. Subsequently, INT-0089 demonstrated that 6 months of adjuvant bolus 5-FU/leucovorin (LV) (Mayo Clinic Schedule or Roswell Park Schedule) showed a similar benefit to 1 year of bolus 5-FU/levamisole, with no further added benefit of concurrent addition of levamisole to an LV-containing regimen.[3]

Studies of the oral fluoropyrimidines capecitabine and uracil and ftorafur (UFT) have demonstrated that each of these is an acceptable alternative to parenteral 5-FU/LV in the adjuvant setting. In a study powered to evaluate noninferiority of capecitabine versus the Mayo Clinic bolus 5-FU/LV schedule, noninferiority was demonstrated.[4] Similar results (noninferiority of an oral fluoropyrimidine vs Mayo Clinic 5-FU/LV) were demonstrated in the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-06 Trial for the oral agent UFT plus oral LV, although UFT is not commercially available in the United States.[5,6]

## OXALIPLATIN-BASED COMBINATION CHEMOTHERAPY REGIMENS

In the Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon cancer (MOSAIC) trial, 2246 patients (60% stage III and 40% stage II) were randomly assigned to receive either bolus plus infusional 5-FU/LV on an every-other-week schedule (LV5FU2), or the same schedule plus oxaliplatin, which results in a regimen known as FOLFOX-4.[7] Updated efficacy results have now been reported (**Table 1**).[8] Five-year disease-free survival (DFS) was 73.3% for the FOLFOX group and 67.4% in the 5-FU/LV group (hazard ratio [HR] = 0.80; 95% confidence interval [CI], 0.68–0.93; $P = .003$). The 6-year overall survival (OS) rates were 78.5% for the FOLFOX group and 76.0% in the 5-FU/LV group (HR = 0.84; 95% CI, 0.71–1.00; $P = .046$); corresponding 6-year OS rates for patients with stage III disease were 72.9% and 68.7%, respectively (HR = 0.80; 95% CI, 0.65–0.97; $P = .023$). No improvement in OS was seen with the addition of oxaliplatin in patients with stage II disease.

Toxicities were notable for a 12% incidence of grade 3 sensory neuropathy, which remained at grade 3 in 1% of the patients at 1-year follow-up. Long-term neurotoxicity is a major concern, with 27% of patients having some residual neurotoxicity 1 year after the end of treatment and 11% of patients having some residual neurotoxicity

**Table 1**
**Efficacy outcomes of FOLFOX versus 5-FU/LV (MOSAIC Trial)**

| | Stage III 6-y OS | Stage III 5-y DFS | Stage II 6-y OS | Stage II 5-y DFS |
|---|---|---|---|---|
| FOLFOX | 72.9% | 66.4% | 85.0% | 83.7% |
| 5-FU/LV | 68.7% | 58.9% | 83.3% | 79.9% |
| *P* Value | $P = .023$ | $P = .005$ | $P = .65$ | $P = .258$ |

*Abbreviations:* DFS, disease-free survival; OS, overall survival.

*Data from* Andre T, Boni C, Navarro M, et al: Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC Trial. J Clin Oncol 2009;27:3109–16.

after 4 years of follow-up. It is reasonable to assume that toxicity, which has not resolved after 4 years, is likely to be permanent.

The NSABP C-07 trial evaluated the addition of oxaliplatin to weekly bolus 5-FU/LV (Roswell Park Schedule), randomly assigning 2407 patients with stage II (29%) or stage III colon cancer to half a year of 5-FU/LV (500 mg/m$^2$ bolus weekly for 6 of every 8 weeks) with or without oxaliplatin (85 mg/m$^2$ administered on weeks 1, 3, and 5 of every 8-week cycle). With median 34-month follow-up, 3-year DFS for the oxaliplatin/bolus 5-FU/LV (FLOX) arm was 77% versus 72% for bolus 5-FU/LV, with corresponding 21% risk reduction (HR 0.79). However, toxicity was prominent in both groups, with high incidences of grade 3 and 4 diarrhea. Hospitalization for diarrhea or dehydration was required in 5% of patients receiving oxaliplatin and 3% of the control group.

More recently, the combination of capecitabine plus oxaliplatin (CapeOx) has been compared with 5-FU/LV in the NO16968 trial.[9] This trial, thus far reported only in abstract form, shows a statistically significant improvement in 3-year DFS (the prespecified primary end point of the trial) for the patients on the CapeOx arm. This result would seem to justify use of CapeOx as an alternative to FOLFOX or FLOX. It should be noted that CapeOx requires a highly reliable, motivated patient to assure adequate and accurate compliance with the medication schedule. Because patients require intravenous administration of oxaliplatin in the CapeOx regimen, it remains a matter of individual subjective judgment as to whether the fully parenteral or parenteral plus oral regimen is more convenient for the patient.

Given the results of the MOSAIC, C-07, and NO16968 trials, oxaliplatin plus a fluoropyrimidine should be regarded as standard adjuvant treatment for completely resected stage III colon cancer and should be regarded as an appropriate consideration for high-risk patients with stage II cancer. Head-to-head comparisons of the FOLFOX and FLOX regimens are not, and will never be, available. However, based on the apparent superior toxicity profile, the FOLFOX regimen is generally preferred. The unreported AVANT trial provides randomized comparison of a FOLFOX and CapeOx-based regimen.

## NEGATIVE TRIALS: IRINOTECAN, BEVACIZUMAB, AND CETUXIMAB

A classic paradigm of drug development has been to establish in the metastatic setting that a combination of a standard treatment plus a new agent is superior to that standard treatment alone. Having established efficacy in the metastatic setting, investigators then move that new regimen into the adjuvant setting to attempt to

increase the cure rate. However, all too often practitioners make the premature decision to adopt such new combinations into their standard adjuvant practice before the adjuvant trials have been completed. As demonstrated by the results of irinotecan, bevacizumab, and cetuximab, all of which are part of the standard management of metastatic disease, such premature conclusions are unwarranted and may place patients at risk of needless and potentially dangerous toxicity.

### *Irinotecan*

Following the demonstration that irinotecan conferred a survival advantage in the metastatic setting, the Cancer and Leukemia Group B Intergroup trial, C89803, evaluated the IFL weekly irinotecan/5-FU/LV bolus schedule compared with the bolus Roswell Park 5-FU/LV schedule in patients with stage III CRC.[10] The addition of irinotecan to bolus 5-FU/LV demonstrated no clinical benefit in either DFS or OS, and a significantly higher early death rate was observed in patients randomized to the IFL arm as well as significant increases in grade 3 or 4 neutropenia and febrile neutropenia.

Similarly disappointing results were seen with the FOLFIRI (biweekly irinotecan plus 48-hour infusional 5-FU) regimen. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) II trial randomized 400 patients with high-risk stage III disease (4 or more nodes positive or obstructed or perforated colon cancers) to biweekly infusional 5-FU/LV with or without irinotecan.[11] With a median follow-up of 36 months, event-free survival was not significantly different between the arms but trended toward inferiority of the irinotecan-containing arm. There were significant imbalances in several important prognostic factors between the arms that favored the control arm; however, even in models adjusting for these imbalances, the irinotecan-containing arm remained nonsignificantly inferior. In a subset analysis of the MOSAIC trial involving FOLFOX, a similar group of high-risk patients with stage III cancer (4 or more positive nodes) actually achieved the most benefit from the addition of oxaliplatin, suggesting that this high-risk group would offer the greatest chance for irinotecan to show a favorable result; yet this irinotecan trial was clearly negative.

The Pan European Trial of Advanced Colon Cancer (PETACC)-3 trial compared biweekly infusional 5-FU/LV to the same regimen plus 180 mg of irinotecan (the FOLFIRI regimen) in 3278 patients, 2333 of who had stage III colon cancer and made up the group that was evaluated for the primary efficacy analysis.[12] There was no significant difference in the prespecified primary end point of the trial, which was 3-year DFS in stage III patients (3-year DFS 63% vs 60%, HR 0.89, $P = .107$). A retrospective evaluation of patients with stage III cancer demonstrated a higher percentage of T4 patients in the irinotecan arm compared with the infusional 5-FU/LV alone arm (n = 180 vs 130 patients, 17% vs 13%). However, it should be noted that T category was not included as a potential prognostic variable for modeling in the protocol; thus its inclusion in the modeling is a post hoc analysis. In this risk-adjusted statistical analysis of the stage III data involving T and N category stratification, a significant DFS (HR 0.85, CI 0.74–0.98, $P = .021$) and relapse-free survival (HR 0.82, CI 0.71–0.95, $P = .009$) was identified. Nonetheless, this trial failed to meet its prespecified statistical primary end point of improvement of DFS. Furthermore, the PETAC-3 trial cannot be interpreted in a vacuum; although aspects of this trial suggest some possibility of modest benefit, the ACCORD II and C89803 trials are strongly negative. Based on the aggregate of these 3 large randomized adjuvant trials, irinotecan-containing chemotherapy appears to be clinically ineffective and should not be used in standard practice in the adjuvant setting.

### *Bevacizumab*

A pivotal placebo-controlled phase III trial of IFL versus IFL plus bevacizumab given at 5 mg/kg every 14 days demonstrated a 4.7-month survival benefit to the group receiving bevacizumab. Rare but serious events, such as gastrointestinal perforation and arterial thrombotic events as well as more common but less serious events such as proteinuria and hypertension, were statistically significantly increased in the group receiving bevacizumab. The NSABP, building on the positive adjuvant trials with oxaliplatin and making the assumption that the benefits of adding bevacizumab to IFL would necessarily translate to oxaliplatin-based therapy as well, conducted a 2700-patient randomized trial of FOLFOX versus FOLFOX plus bevacizumab. After the start of this trial, a 1400-patient randomized trial of oxaliplatin-based first-line therapy for metastatic disease plus or minus bevacizumab,[13] although showing a modest, albeit statistically significant 1.4-month improvement in progression-free survival, failed to show either a statistically or clinically significant survival benefit, and the trial showed absolutely no response benefit, raising concerns about the utility of bevacizumab in the adjuvant setting. In a maneuver that is difficult to justify, the NSABP chose to lengthen the duration of bevacizumab to 1 full year. Thus, the trial was 6 months of FOLFOX versus 6 months of FOLFOX plus bevacizumab followed by an additional 6 months of bevacizumab alone.

Had this trial produced a positive result it would, in all likelihood, have been impossible to ever conduct a trial to determine if the additional 6 months of bevacizumab contributed to the outcome. However, that problem did not arise because this trial, reported thus far in abstract form, is negative, having failed to meet its prespecified primary end point of improved 3-year DFS.[14] There was an interesting, albeit clinically irrelevant improvement in DFS at 1 year, suggesting that the indefinite continuation of bevacizumab might improve cancer-specific outcome; however, the toxicity and expense of such prolonged bevacizumab exposure make evaluation or use of such an approach unreasonable. At this time, there is no role for the use of bevacizumab in the adjuvant setting of colon cancer.

### *Cetuximab*

Clinical trials with cetuximab had demonstrated antitumor responses when given both as a single agent and in conjunction with chemotherapy. The North Central Cancer Treatment Group (NCCTG) initiated a phase 3 trial of FOLFOX plus or minus cetuximab in patients with stage III colon cancer. After the start of the trial, only tumors that harbored mutations in the Kirsten rat sarcoma (KRAS) gene were potentially sensitive to cetuximab, and the trial was restructured to further enroll only those patients whose tumors had these mutations. In the autumn of 2009, the Data Safety Monitoring Committee of the NCCTG informed investigators that the trial was being immediately halted because of its futility. A presentation of the data in abstract form revealed no benefit in 3-year DFS or OS with the addition of cetuximab, even to patients with tumors that do not have KRAS mutations.[15] The data from a European trial, PETACC-8, are still maturing; however, at this time it is not appropriate to use cetuximab in the adjuvant setting.

## STAGE II COLON CANCER

The utility of adjuvant chemotherapy for patients with stage II colon cancer remains controversial. Stage II CRC (T3–4N0M0) makes up approximately a quarter of newly diagnosed CRC patients and has a good prognosis, with a 72% to 85% OS. However, for high-risk patients with stage II cancer, with either clinical obstruction, perforation,

poorly differentiated histology, lymphovascular invasion, or inadequate lymph node sampling (<10 nodes), a generally poorer prognosis can be expected, with an approximate 5-year DFS estimate of 60% to 70%. Although there are no definitive data showing treatment benefit in this group, most data suggest, and most clinicians believe, that such patients are appropriate for treatment along the lines of patients with stage III cancer. Microsatellite instability (MSI) and absence of loss of heterozygosity (LOH) of 18q have been suggested to be favorable prognostic markers, possibly avoiding adjuvant therapy, and are discussed under the heading of molecular markers in later discussion.

A subset analysis of 318 patients with stage II cancer in US Intergroup 0035, randomized to receive either 5-FU and levamisole or surgery alone, demonstrated no difference in 7-year survival rates, 72% for both groups ($P = .83$).[16]

The quick and simple and reliable (QUASAR) adjuvant trial from the United Kingdom, involving 3289 predominately (91%) patients with stage II CRC with "uncertain indications for adjuvant treatment," 71% of whom had colon as opposed to rectal cancer, demonstrated a modest but statistically significant reduction in recurrence rate (22.2% vs 26.2%; HR 0.78, 95% CI, 0.67–0.91) and an improvement in 5-year survival rate (80.3% vs 77.4%; HR 0.83, 95% CI, 0.71–0.97) with adjuvant chemotherapy compared with observation.[17] In the IMPACT (International Multicenter Pooled Analysis of Colon Cancer Trial) study, a pooled analysis of 5 European trials involving 1016 patients with stage II colon cancer randomized to adjuvant 5-FU/LV versus observation showed a 5-year survival of 82% versus 80%, respectively.[18] This analysis trended strongly toward, but did not reach, statistical significance.

The Surveillance, Epidemiology, and End-Results Medicare Analysis identified 3151 patients with stage II cancer, with no high-risk features using the Medicare database.[19] Approximately 27% of these elderly Medicare patients received adjuvant chemotherapy (predominately 5-FU/LV). With an OS rate of 78% for chemotherapy patients versus 75% for observed patients, this nonrandomized analysis suggests minimal benefit of adjuvant chemotherapy for patients with stage II CRC.

Multiple meta-analyses have attempted to determine the benefit of chemotherapy in patients with stage II CRC: the pooled Intergroup Meta-analysis evaluated 3302 stage II and III patients with colon cancer from 7 randomized trials comparing adjuvant 5-FU/LV or 5-FU/levamisole versus observation.[20] Patients with stage II colon cancer did not demonstrate a survival advantage (81% vs 80%, $P = .113$) in this analysis.

The Cancer Care Ontario Practice Guideline Initiative Gastrointestinal Cancer Disease Site Group systematically reviewed 37 trials and 11 meta-analyses published after 1987.[21] A separate meta-analysis sanctioned by American Society of Clinical Oncology was performed on a subset of 12 trials (4187 patients) with an observation arm and at least one 5-FU–based adjuvant chemotherapy arm for patients with stage II colon cancer.[22] The mortality risk ratio for patients with stage II CRC did not reach statistical significance (HR 0.87, 95% CI, 0.75–1.10, $P = .07$).

A subset analysis of the MOSAIC Trial demonstrated no statistically significant advantage of the addition of oxaliplatin to LV5FU2 in patients with stage II cancer; however, this subset was too small to adequately address this question.[7] However, in the 12% (108 of 899) of patients with stage II cancer with high-risk features (T4 primary, perforation, obstruction, or vascular invasion), a strong trend toward improved outcome with the addition of oxaliplatin was seen.

## MOLECULAR MARKERS

At present, there are no validated markers to assist in the selection of either patients who do or do not need chemotherapy, or specific chemotherapy agents, for an

individual patient in the adjuvant setting. The Eastern Cooperative Oncology Group E5202 trial is evaluating the role of chemotherapy in higher-risk patients with stage II CRC as defined by the absence of high MSI and intact 18q status. Patients with microsatellite stable disease and/or LOH at chromosome 18q are assigned to treatment with modified FOLFOX-6 and randomized to receive bevacizumab or not, whereas patients with high MSI and no 18q LOH are assigned to the observation alone arm. Accrual is continuing.

Some studies have suggested that tumors with high MSI (either by direct measurement or by demonstration of deficient mismatch repair protein [MMR] on immunohistochemical staining) do not benefit, or may even suffer a detriment, from 5-FU/LV. An analysis of MSI from archival tissues from 4 NSABP adjuvant chemotherapy trials demonstrated no prognostic correlation and no trend toward a correlation between high MSI and OS ($P = .67$).[23] However, more recently, Sargent and colleagues[24] reported on 457 stage II or III patients with colon cancer, with tumor samples available, who were randomized to 5-FU–based chemotherapy versus observation in National Cancer Institute cooperative group trials (**Table 2**). Fifteen percent of these patients were found to have tumors that were MMR deficient. In patients with these MMR-deficient tumors, no benefit from 5-FU was seen in DFS. In patients with stage II cancer, with MMR-deficient tumors, treatment with 5-FU was associated with decreased OS. These data support the use of MMR evaluation in patients with stage II cancer and indicate that single-agent fluoropyrimidine should not be used in patients with MMR-deficient tumors. Because oxaliplatin was not available and therefore not used in the patients studied, these data do not comment on the role of MMR in the effectiveness of FOLFOX or other oxaliplatin-containing regimens.

Pharmacogenomic studies are attempting to identify those patients who may be at higher risk of toxicity from specific agents. These studies may identify subgroups for whom one therapy or another is more effective or safer, or both. However, this remains an investigational approach at this time.

## SUMMARY AND CLINICAL RECOMMENDATIONS

The FOLFOX regimen is the current regimen of choice for patients with stage III cancer and for at least high-risk patients with stage II cancer. Although the FOLFOX-4 regimen was involved in the registration trial, the modified FOLFOX-6 regimen, with a simplified 5-FU/LV dosing schedule compared with FOLFOX-, is what is most widely used in practice. Modified FOLFOX-6 has served as the basis for the most recent US Cooperative Group studies involving the FOLFOX regimen. The CapeOx and FLOX

**Table 2**
**Mismatch repair status as a predictor of benefit from 5-FU**

| MMR Status | Treatment Arm | 5-y DFS (%) | *P* value |
|---|---|---|---|
| MMR-deficient | Observation | 76 | $P = .56$ |
| N = 70 | 5-FU | 72 | |
| MMR-proficient | Observation | 53 | $P = .02$ |
| N = 387 | 5-FU | 64 | |

*Data from* Sargent DJ, Marsoni S, Monges G, et al: Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol 2010;28:3219–26.

regimens are acceptable alternatives. Trials of irinotecan, bevacizumab, and cetuximab have been negative in the adjuvant setting. Therefore, these agents should not be used for this purpose. In those patients who are not considered appropriate for oxaliplatin-based therapy, either 5-FU/LV, or the oral fluoropyrimidines capecitabine or UFT plus leucovorin would seem to be reasonable options.

Adjuvant chemotherapy for stage II colon cancer remains a topic of some controversy. Virtually all patients with stage II cancer deserve a medical oncology consultation for a frank discussion of the potential benefits, including a realistic assessment of the relatively small, but potentially real, incremental benefits of treatment. The decision to give adjuvant chemotherapy to low-risk patients with stage II colon cancer should be an informed decision comparing a possible OS advantage of at most 2% to 4% and a 0.5% to 1% risk of mortality with chemotherapy, in addition to chemotherapy-related morbidities. The available clinical trials and meta-analyses do not clearly settle the issue for or against adjuvant chemotherapy for low-risk patients with stage II colon cancer; however, evidence suggests that patients with tumors showing deficient MMR proteins should not be treated with single-agent fluoropyrimidines.

No molecular markers have been shown to be clearly of benefit in selecting patients for adjuvant therapy at this time, as attempts to develop a gene signature to identify those patients who do or do not need treatment have thus far been unsuccessful. At present, there is no utility to molecular analysis (other than MMR as mentioned earlier) in the management of patients with stage II and III cancer.

## REFERENCES

1. Greene F, Stewart A, Norton H. A new TNM staging strategy for node-positive (stage III) colon cancer: an analysis of 50,042 patients. Ann Surg 2002;236: 416–21.
2. Moertel C, Fleming T, Macdonald J, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 1990;322:352.
3. Haller DG, Catalano PJ, Macdonald JS, et al. Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089. J Clin Oncol 2005;23:8671–8.
4. Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 2001;19:4097–106.
5. Saltz LB, Leichman CG, Young CW, et al. A fixed-ratio combination of uracil and ftorafur (UFT) with low dose leucovorin. An active oral regimen for advanced colorectal cancer. Cancer 1995;75:782–5.
6. Lembersky BC, Wieand HS, Petrelli NJ, et al. Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project Protocol C-06. J Clin Oncol 2006;24:2059–64.
7. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343–51.
8. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009;27:3109–16.
9. Haller D, Tabernero J, Maroun J, et al. 5LBA First efficacy findings from a randomized phase III trial of capecitabine + oxaliplatin vs. bolus 5-FU/LV for stage III colon cancer (NO16968/XELOXA study). Proceedings of European Society of Medical Oncology (ESMO) 2009;7:4.

10. Saltz LB, Neidzweicki D, Hollis D, et al. Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: results of CALGB 89803. J Clin Oncol 2007;25:3456–61.
11. Ychou M, Raoul J, Douillard JY, et al. A phase III randomised trial of LV5FU2 + irinotecan versus LV5FU2 alone in adjuvant high-risk colon cancer (FNCLCC Accord02/FFCD9802). Ann Oncol 2009;20:674–80.
12. Van Cutsem E, Labianca R, Hossfeld G, et al. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. J Clin Oncol 2009; 27:3117–25.
13. Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26:2013–9.
14. Wolmark N, Yothers G, O'Connell MJ, et al. A phase III trial comparing mFOLFOX6 to mFOLFOX6 plus bevacizumab in stage II or III carcinoma of the colon: results of NSABP protocol C-08 [abstract]. J Clin Oncol 2009;27(Suppl):LBA4.
15. Alberts SR, Sargent DJ, Smyrk CJ, et al. Adjuvant mFOLFOX6 with or without cetuximab (Cmab) in KRAS wild-type (WT) patients (pts) with resected stage III colon cancer (CC): results from NCCTG intergroup phase III trial N0147 [abstract]. J Clin Oncol 2010;28(Suppl):CRA3507.
16. Moertel CG, Fleming TR, Macdonald JS, et al. Intergroup study of fluorouracil plus levamisole as adjuvant therapy for stage II/Duke's B2 colon cancer. J Clin Oncol 1995;13:2936–43.
17. QUASAR Collaborative Group. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet 2007;370:2020–9.
18. Aarnio M, Sankila R, Pukkala E, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer 1999;81:214–8.
19. Schrag D, Rifas-Shiman S, Saltz L, et al. Adjuvant chemotherapy use for Medicare beneficiaries with stage II colon cancer. J Clin Oncol 2002;20:3999–4005.
20. Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol 2004;22:1797–806.
21. Figueredo A, Charette ML, Maroun J, et al. Adjuvant therapy for stage II colon cancer: a systematic review from the cancer care Ontario program in evidence-based care's gastrointestinal cancer disease site group. J Clin Oncol 2004;22:3395–407.
22. Benson AB 3rd, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004;22:3408–19.
23. Kim GP, Colangelo LH, Wieand HS, et al. Prognostic and predictive roles of high-degree microsatellite instability in colon cancer: a national cancer institute-national surgical adjuvant breast and bowel project collaborative study. J Clin Oncol 2007;25:767–72.
24. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol 2010;28:3219–26.