CCU | 2005 VOL 4 | ISSUE 1

Colorectal Cancer™ UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

EDITOR

Neil Love, MD

FACULTY INTERVIEWS

Chris Twelves, MD

Norman Wolmark, MD

Howard S Hochster, MD

CME Certified

www.ColorectalCancerUpdate.com

Colorectal Cancer Update
A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

Colorectal cancer is among the most common cancers in the United States, and the arena of colorectal cancer treatment continues to evolve. Published results from ongoing clinical trials lead to the emergence of new therapeutic agents and regimens and changes in indications, doses and schedules for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these advances.

To bridge the gap between research and patient care, *Colorectal Cancer Update* utilizes one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME activity assists medical oncologists in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment and incorporate these data into management strategies in the local and advanced disease settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including the use of oxaliplatin- and capecitabine-containing regimens, and explain the absolute risks and benefits of adjuvant chemotherapy regimens to patients.
- Integrate emerging data on biologic therapies into management strategies for patients with advanced colorectal cancer.

PURPOSE OF THIS ISSUE OF *COLORECTAL CANCER UPDATE*

The purpose of Issue 1 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Twelves, Wolmark and Hochster on the integration of emerging clinical research data into the management of colorectal cancer.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 3 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

HOW TO USE THIS MONOGRAPH

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **ColorectalCancerUpdate.com** offers an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **red underlined text**.

Table of Contents

DISCLOSURES

As a provider accredited by the Accreditation Council for Continuing Medical Education, it is the policy of Research To Practice to require the disclosure of any significant financial interest or any other relationship the sponsor or faculty members have with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The presenting faculty reported the following:

Dr Twelves – **Grants/Research Support:** AstraZeneca Pharmaceuticals LP, KuDOS Pharmaceuticals, Pfizer Inc, Roche Laboratories Inc, SuperGen Inc; **Consultant and Speakers Bureau:** Roche Laboratories Inc

Dr Wolmark – No financial interests or affiliations to disclose

Dr Hochster – **Consultant:** Genentech BioOncology, Novartis Pharmaceuticals, Sanofi-Aventis

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantor.

UPCOMING EDUCATIONAL EVENTS

2005 American Society of Clinical Oncology Prostate Cancer Symposium: February 17-19, 2005

Hyatt Grand Cypress
One Grand Cypress Blvd
Orlando, Florida
Event website: www.asco.org/ac/1,1003,_12-002665-00_18-0034689,00.asp

Miami Breast Cancer Conference: February 23-26, 2005

Loews South Beach
1601 Collins Avenue
Miami Beach, Florida
Event website:
www.cancerconf.com/index.html

10th National Comprehensive Cancer Network Annual Conference: March 16-20, 2005

Westin Diplomat
3555 South Ocean Drive,
Hollywood, Florida
Event website: www.nccn.org/professionals/meetings/10thannual/default.asp

96th Annual Meeting of the American Association for Cancer Research: April 16-20, 2005

Anaheim, California
Event website:
www.aacr.org/2005AM/2005AM.asp

Oncology Nursing Society; 30th Annual Congress: April 28-May 1, 2005

Orlando, Florida
Event website: www.ons.org/nursingEd/Conferences/congress.shtml

41st American Society of Clinical Oncology Annual Meeting: May 13-17, 2005

Orange County Convention Center
Orlando, Florida
Event website: www.asco.org/ac/1,1003,_12-002092,00.asp

2005 American Society for Therapeutic Radiology and Oncology Annual Meeting: October 16-20, 2005

Denver, Colorado
Event website:
www.astro.org/annual_meeting/

2005 San Antonio Breast Cancer Symposium: December 2005

San Antonio, Texas
Event website:
www.sabcs.org/Index.asp

Editor's Note

The whole truth and nothing but the truth

(Sub-editor's note: I recently authored several abstracts for submission to ASCO and ONS and have developed a mild addiction to abbreviation. I apologize for this.)

One of the most exciting aspects of my unexpectedly "different" oncologic career has been the opportunity to listen to people with integrity tell it like it is. It has come to the point where I know in advance that during some of my interviews with research leaders (RLs), I will silently ask myself, "Did I just hear what I thought I heard?" Any interview with Norman Wolmark is guaranteed to provide a number of such moments, and for this issue, he does not disappoint.

What does Norm think about the fact that many RLs and a recent ASCO position paper do not support adjuvant chemotherapy in Stage B colon cancer patients? (Norm vehemently disagrees [NVD].) What about the fact that the FDA has not made UFT available as an option for patients in the United States? (NVD.) How does Norm respond to RLs who say that the new NSABP trial evaluating intrahepatic FUDR is asking an antiquated research question? (NVD.) The list goes on.

While Norm's propensity not to pull punches is commendable, don't think for a second that every RL does the same. We recently audio recorded a tumor panel discussion during which a RL spat out a diatribe blasting a recent clinical trial report from a major cancer institution in Texas. My excitement at hearing these words was balanced by the fact that I also knew that this RL is one of the very few who likes to review the final edited audio script before we send out the program.

Sure enough, after sending the script, we received back a wry email comment from this RL about not wanting to be vilified by the entire ASCO membership. The RL requested that we delete those specific comments from the edited audio program. Okay, whatever, maybe it was for the best as it probably prevented some of our listeners from driving off the road when they heard this perspective.

In another recent educational adventure, I was querying a well-spoken RL about the role of capecitabine in cancer treatment. The interviewee believed that this fascinating oral agent is vastly underutilized in practice. When I asked about the etiology of this phenomenon, the RL said, "because oncologists make more money on injectable chemotherapy."

I took a very deep breath (a gasp, actually) and we went on to chat about this for 10 minutes, during which I was educated on the practicalities of oncologic business.

I had heard only one other RL make a similar comment for the record — Ed Chu in this series — and while I was contemplating the response we might receive to the statements of this brave new soul, a light bulb seemed to go off in the RL's brain. "This isn't going to be on the program, is it?" And it wasn't, which disappointed the hell out of me.

Somewhere out there, new champions of truth await us. Maybe an individual who will discuss the economics of LHRH agonists in prostate cancer treatment and why men with this disease don't realistically have the option of bicalutamide 150 mg as oral monotherapy. This antiandrogen regimen — which results in more than five times the out-of-pocket cost as an aromatase inhibitor in breast cancer — seems to cause far less asthenia, erectile dysfunction, and vasomotor symptoms than chemical castration. At 50 mg, combined with an LHRH agonist, survival is improved by 20% compared to an LHRH agonist alone. Yet, the personal financial burden of this noncovered expense prevents urologists from even raising the option to most patients. Men deserve better than this, but no one seems to care much about it.

Perhaps all is not lost. Recently, our group held a closed roundtable discussion on prostate cancer with a dozen urologists, radiation oncologists and medical oncologists. For once, there was no BS, and the cold harsh truth of the economics of practice was discussed openly and for the record. It was refreshing, honest, open, and scary...and probably happened for one reason: these physicians were also prostate cancer patients.

— Neil Love, MD
NLove@ResearchToPractice.net

Select publications

Andre T et al. **Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer.** *N Engl J Med* 2004;350(23):2343-51. **Abstract**

Benson AB 3rd et al. **American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer.** *J Clin Oncol* 2004;22(16):3408-19. **Abstract**

Cassidy J et al. **Capecitabine (X) vs bolus 5-FU/leucovorin (LV) as adjuvant therapy for colon cancer (the X-ACT study): Efficacy results of a phase III trial.** *Proc ASCO* 2004;**Abstract 3509**.

De Gramont A et al. **Oxaliplatin/5-FU/LV in adjuvant colon cancer: Results of the international randomized mosaic trial.** *Proc ASCO* 2003;**Abstract 1015**.

Saltz L et al. **Irinotecan plus fluorouracil/leucovorin (IFL) versus fluorouracil/leucovorin alone (FL) in stage III colon cancer (Intergroup trial CALGB C89803).** *Proc ASCO* 2004;**Abstract 3500**.

Scheithauer W et al; X-ACT Study Group. **Oral capecitabine as an alternative to i.v. 5-fluorouracil-based adjuvant therapy for colon cancer: Safety results of a randomized, phase III trial.** *Ann Oncol* 2003;14(12):1735-43. **Abstract**

Wolmark N et al. **A phase III trial comparing oral UFT to FULV in stage II and III carcinoma of the colon: Results of NSABP Protocol C-06.** *Proc ASCO* 2004;**Abstract 3508**.

X-ACT adjuvant trial

Trial design and eligibility

The X-ACT trial (Cassidy 2004b) compared capecitabine versus bolus 5-FU/leucovorin as adjuvant therapy for colon cancer. Designed to mirror the metastatic trial, we hoped to prove that capecitabine was at least as effective in terms of disease-free survival, relapse-free survival and overall survival. The trial was multinational with 2,000 patients and it was limited to patients with Dukes' C colon cancer. We excluded patients with rectal cancer because it's biologically different, and the role of adjuvant therapy in rectal cancer is less clear.

We chose Dukes' C because the rationale for and the benefits of adjuvant chemotherapy are clearer in patients with this disease stage. Specifically, the benefits of adjuvant 5-FU in Dukes' C disease are quite significant and well demonstrated, so this criteria ensured a rigorous test for capecitabine. We were concerned that if we allowed patients with Dukes' B disease, the study would be underpowered because a larger proportion of these patients are cured by surgery alone, and therefore, the benefits of 5-FU would be more subtle.

Efficacy data

The predetermined aim of the trial was to show equivalence in terms of disease-free survival, and that was achieved with a *p*-value of less than 0.0001. We designed the protocol so that if we achieved the primary endpoint, a secondary analysis of superiority could be triggered. This analysis was, indeed, performed on disease-free survival, and it just failed to reach statistical significance with a *p*-value of 0.05. However, the fact that we almost reached the secondary goal of showing superiority is a reflection of the degree by which we exceeded our stated endpoint.

Capecitabine reduced the risk of death by 16 percent and reduced the risk of recurrence by 14 percent. The relapse-free survival favored capecitabine with a statistically significant *p*-value of less than 0.05. The distinction between disease-free and relapse-free survival is subtle — disease-free survival includes other-cause deaths.

Dr Twelves is the NTRAC Professor of Clinical Cancer Pharmacology and Oncology at the University of Leeds and Bradford NHS Hospitals Trust in Bradford, United Kingdom.

Not only did the disease-free, relapse-free and overall survival favor capecitabine, when we performed the multivariate analysis examining the prognostic factors that predict these outcomes, in each case the allocated treatment, capecitabine, was one of the factors that significantly influenced these endpoints. In terms of efficacy, adjuvant capecitabine proved to be at least as effective as, and may well be more effective than, bolus 5-FU/leucovorin.

Within our practice, a proportion of patients will be treated with combination chemotherapy as part of their adjuvant therapy, but it's unlikely that will apply to all patients. Patients tolerate treatment differently and not all patients have the same risk of recurrence. I believe there will continue to be a role for single-agent fluoropyrimidines and, in that setting, there's a strong argument now that capecitabine should replace the Mayo regimen. It's at least as effective and more tolerable.

Safety data

The initial dose for capecitabine was 2,500 mg/m^2, total dose per day, 14 days on, seven days off, and many patients required dose reductions. The proportion of patients requiring a dose reduction was very similar for the two arms of the study — 42 versus 44 percent for capecitabine versus 5-FU/leucovorin, respectively. When we evaluated the number of patients experiencing treatment interruptions, there were more with capecitabine, as we would expect.

We view that as one of the advantages of capecitabine, in that this 14-day administration allows more opportunity to adjust the dose as needed. Overall, the pattern of toxicities favored capecitabine — there was less diarrhea, stomatitis, alopecia and myelosuppression (1.1). The only toxicity that increased with capecitabine was hand-foot syndrome, which we are now experienced at preventing and managing.

1.1 X-ACT Trial Safety Data: Treatment-Related Adverse Events (All Grades) and Lab Abnormalities (Grades III and IV) > 15% in Patients ≥ 70 Years of Age

	Capecitabine (n=186)	5-FU/leucovorin (n=205)
Diarrhea	52%	68%
Stomatitis	23%	67%
Nausea	33%	47%
Fatigue	17%	19%
Hand-foot syndrome	63%	8%
Neutropenia	4%	31%
Hyperbilirubinemia (NCIC CTC)*	17%	5%

* Hyperbilirubinemia was minimal in both arms when graded by NCI CTCAE (Common Terminology Criteria for Adverse Events).

SOURCE: Díaz-Rubio E et al. **Safety of capecitabine (X) compared to fluorouracil/leucovorin (5-FU/LV) for the adjuvant treatment of elderly colon cancer patients (pts).** *Proc ASCO* 2004; **Abstract 3737**.

Pharmacoeconomic analysis

Interestingly, when we did a pharmacoeconomic analysis based upon practice in the UK, we were able to show a substantial financial savings. Although the cost of capecitabine is greater, it is more than offset by the reductions in administration costs and the costs of managing adverse events. We are in the fortunate position of finding that not only is capecitabine probably more effective, but it is also less expensive than the current standard treatment (McKendrick 2004).

Capecitabine plus oxaliplatin in the treatment of metastatic disease

We have published Phase II data that show capecitabine/oxaliplatin (CAPOX) to be active as a first-line therapy for patients with metastatic colorectal cancer (Cassidy 2004a) (1.2). While this was not a randomized trial, there were nearly 100 patients and it was carried out in a number of centers. The data is quite robust compared to a small, single-institution study.

The overall objective response rate was approximately 55 percent and when we analyzed subgroups — such as age and sites of metastases — we saw very similar response rates in these groups. We also found that patients aged 65 and older were similarly as tolerant of the CAPOX regimen as younger patients, so we're encouraged that this regimen can be used in a broader population and not just in the younger or fitter patients.

There have been a number of studies evaluating different schedules of CAPOX and different combinations with capecitabine in the metastatic setting, and they have broadly similar results. The studies of capecitabine/oxaliplatin and the capecitabine/irinotecan combinations demonstrate response rates of approximately 50 percent. Both combinations are well tolerated provided the appropriate dose modifications are made. Given the range of different combinations, settings and varying schedules for these studies, the data are astonishingly robust.

1.2 Clinical Trial of Capecitabine Plus Oxaliplatin as First-Line Therapy for Patients with Metastatic Colorectal Cancer: Efficacy Data

Tumor response*	Number	Percent	95% CI
Objective response (CR + PR)	53	55	45 to 65%
Stable disease	30	31	22 to 42%
Progressive disease	6	6	2 to 13%
Not assessable†	7	7	3 to 14%

* Investigator-intent-to-treat population
† Patients without post-baseline tumor assessment
CR = complete response; PR = partial response

SOURCE: Cassidy J et al. **Xelox (capecitabine plus oxaliplatin): Active first-line therapy for patients with metastatic colorectal cancer.** *J Clin Oncol* 2004;22(11):2084-91. **Abstract**

Off-protocol use of CAPOX in the adjuvant and metastatic settings

As one who participates in clinical trials, I prefer to wait for evidence from randomized studies before using new combinations off-protocol in the adjuvant and metastatic settings. However, with CAPOX I'm torn because everything we've seen to date from the clinical trials suggests that 5-FU can be substituted with capecitabine in these clinical settings. In addition, I would be very surprised if CAPOX doesn't emerge as being equivalent to the FOLFOX regimen, alone or in combination with bevacizumab.

The broader question is, just how many times do we need to demonstrate the equivalence of 5-FU and capecitabine? We have used 5-FU in many different diseases and different combinations, and there has to be a limit, at least from the regulatory standpoint, to how many times equivalence has to be proven. I do believe CAPOX, off-protocol, is a reasonable option at this time.

MOSAIC adjuvant trial

In the MOSAIC trial, the addition of oxaliplatin data resulted in a significant reduction in the risk of recurrence in the adjuvant setting (André 2004) (1.3). While the survival data is not yet mature, Sargent's data, derived from a wide range of trials, clearly demonstrate that a delay in recurrence ultimately translates into prolonged survival (Sargent 2004).

Although the data are preliminary, I believe the MOSAIC data are the new gold standard. Only time will tell what that means for individual patients. A gold standard doesn't necessarily mean the therapy applies to all patients. There are toxicities related to oxaliplatin, such as myelosuppression and neurotoxicity, and I don't believe oxaliplatin-based adjuvant therapy will replace single-agent treatment across the board.

1.3 Use of Disease-Free Survival as a Primary Endpoint in MOSAIC Trial

"We chose disease-free survival as the primary endpoint of the study because, like others, we believe that the absence of relapse is the best indicator of efficacy, since it relates directly to the effect of the treatment under investigation. By allowing early appraisal of the results, the use of three-year disease-free survival as the primary end point for adjuvant trials of patients with colon cancer should permit rapid evaluation of new treatments.

"Whether disease-free survival should be a primary end point is still under discussion, but a recent analysis of several studies supports the appropriateness of the use of three-year disease-free survival as a good predictor of five-year overall survival in trials of adjuvant treatment of colon cancer."

SOURCE: Andre T et al. *N Engl J Med* 2004;350:2343-51. **Abstract**

I anticipate a rapid move towards oxaliplatin-based treatments, especially in the younger, fitter and higher-risk patients. However, I believe a single-agent fluoropyrimidine will still be an appropriate option for a substantial proportion of older, more frail patients or patients at lower risk of disease recurrence.

Intravenous 5-FU therapy in the adjuvant setting

It's difficult to identify a major role for intravenous 5-FU alone in the adjuvant setting as opposed to capecitabine. There will be some patients who are unable or unwilling to take tablets, or who can't be relied upon to take oral medications. The point I often make is that if we had developed capecitabine first, no one would have developed intravenous 5-FU. Capecitabine has the convenience of an oral treatment that is at least as effective as 5-FU, and I believe it will increasingly become the backbone of treatment in colorectal and breast cancer.

Select publications

André T et al. Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. **Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer.** *N Engl J Med* 2004;350(23):2343-51. **Abstract**

Cassidy J et al. **XELOX (capecitabine plus oxaliplatin): Active first-line therapy for patients with metastatic colorectal cancer.** *J Clin Oncol* 2004a;22(11):2084-91. **Abstract**

Cassidy J et al. **Capecitabine (X) vs bolus 5-FU/leucovorin (LV) as adjuvant therapy for colon cancer (the X-ACT study): Efficacy results of a phase III trial.** *Proc ASCO* 2004b;**Abstract 3509**.

De Gramont A et al. **Oxaliplatin/5-FU/LV in adjuvant colon cancer: Results of the international randomized mosaic trial.** *Proc ASCO* 2003;**Abstract 1015**.

Díaz-Rubio E et al. **Safety of capecitabine (X) compared to fluorouracil/leucovorin (5-FU/LV) for the adjuvant treatment of elderly colon cancer patients (pts).** *Proc ASCO* 2004;**Abstract 3737**.

Giantonio BJ et al. **The addition of bevacizumab (anti-VEGF) to FOLFOX4 in previously treated advanced colorectal cancer (advCRC): An updated interim toxicity analysis of the Eastern Cooperative Oncology Group (ECOG) study E3200.** *Proc ASCO* GI Symposium 2004; **Abstract 241**.

Hurwitz H et al. **Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) prolongs survival in first-line colorectal cancer (CRC): Results of a phase III trial of bevacizumab in combination with bolus IFL (irinotecan, 5-fluorouracil, leucovorin) as first-line therapy in subjects with metastatic CRC.** *Proc ASCO* 2003;**Abstract 3646**.

Hurwitz H et al. **Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.** *N Engl J Med* 2004;350(23):2335-42. **Abstract**

McKendrick JJ et al. **Capecitabine (X) is resource saving compared with i.v. bolus 5-FU/LV in adjuvant chemotherapy for Dukes' C colon cancer patients: Medical resource utilization (MRU) data from a large phase III trial (X-ACT).** *Proc ASCO* 2004;**Abstract 3578**.

Sargent DJ et al. **Disease-free survival (DFS) vs overall survival (OS) as a primary endpoint for adjuvant colon cancer studies: Individual patient data from 12,915 patients on 15 randomized trials.** *Proc ASCO* 2004;**Abstract 3502**.

Scheithauer W et al. **Oral capecitabine as an alternative to i.v. 5-fluorouracil-based adjuvant therapy for colon cancer: Safety results of a randomized, phase III trial.** *Ann Oncol* 2003;14(12):1735-43. **Abstract**

Twelves C et al. **XELOX (capecitabine plus oxaliplatin), a safe and active first-line regimen for elderly patients with metastatic colorectal cancer (MCRC): Post-hoc analysis of a large phase II study.** *Proc ASCO* 2004;**Abstract 3555**.

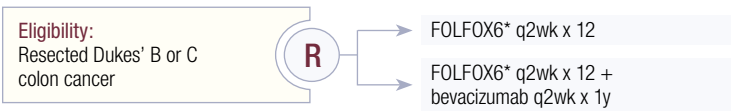
NSABP-C-08: Phase III randomized trial of adjuvant FOLFOX with or without bevacizumab

NSABP-C-08 was opened in October 2004, which from a regulatory standpoint is certainly a major accomplishment. The trial design is simple and straightforward — modified FOLFOX-6 with or without one year of bevacizumab. The eligibility criteria include patients with Dukes' B or C colon cancer (2.1).

Originally, we wanted to make this trial as broad-based as possible and include FLOX (bolus 5-FU/leucovorin/oxaliplatin). The FDA didn't particularly embrace that idea; their response was justified because we didn't have data from NSABP-C-07. In view of the MOSAIC adjuvant trial data with a FOLFOX regimen (Andre 2004), I think a FOLFOX-inspired regimen is reasonable. So, we eliminated the possibility of having FLOX as a control arm. Also, we were thinking of including a capecitabine/oxaliplatin (CAPOX) arm, but the sample size would have been much greater.

2.1 Phase III Randomized Study of Adjuvant FOLFOX with or without Bevacizumab in Patients with Resected Dukes' B or C Colon Cancer

Protocol ID: NSABP-C-08
Target Accrual: 2,632 (Open)



* Modified FOLFOX6

Study Contact:
Carmen Allegra, MD
Email: callegra@nmcr.com
National Surgical Adjuvant Breast and Bowel Project

SOURCE: NCI Physician Data Query, December 2004

Dr Wolmark is Chairman of the Department of Human Oncology at Allegheny General Hospital, Professor and Chairman at Drexel University College of Medicine and Chairman of the National Surgical Adjuvant Breast and Bowel Project in Pittsburgh, Pennsylvania.

Objectives of NSABP-C-08

We really wanted to address a pivotal question — whether the benefits associated with bevacizumab as first-line therapy for metastatic colorectal cancer can be translated to the adjuvant setting. Once we came to grips with that as our unequivocal principal aim, the trial was structured to address it. The sample size is manageable at about 2,600 patients. Theoretically, we hope bevacizumab will be more effective in the adjuvant setting. We hope the prolongation in time to progression seen in patients with advanced disease, if translated to the adjuvant setting, will result in lives saved.

Three-year disease-free survival as a surrogate endpoint in adjuvant trials

We strongly support three-year disease-free survival as a primary endpoint in adjuvant trials. Based upon the NSABP studies, we simply accepted that most of the events in patients with carcinoma of the colon occur within three years. I think we made an error in not disseminating that information widely and not recognizing that this information could have a significant impact.

Dan Sargent, in his combined analysis of 15 trials, unequivocally demonstrated that three-year disease-free survival was an excellent surrogate for five-year survival (Sargent 2004). Unlike patients with breast cancer, most of the cancer events that occur in patients with colon cancer occur within the first three years.

We're very comfortable utilizing three-year disease-free survival as an endpoint for carcinoma of the colon, and I think more importantly, the FDA is comfortable with that endpoint. Virtually all of the trials that are currently ongoing and those that will be started, at least in the United States, are going to focus on disease-free survival.

NSABP-C-06: Phase III randomized adjuvant trial comparing oral UFT with leucovorin to 5-FU/leucovorin

We randomly assigned over 1,000 patients with Dukes' B or C colon cancer to this trial. No differences were seen in disease-free and overall survival (Wolmark 2004). The results from NSABP-C-06, I think, are of interest.

UFT is not FDA approved, and it is not available in the United States. When Bristol-Myers Squibb went before the FDA to obtain an indication for UFT as first-line therapy in patients with metastatic colorectal cancer, two trials were reported — one by Douillard (Douillard 2002) and the other by Carmichael (Carmichael 2002).

Despite a unanimous ODAC (Oncologic Drugs Advisory Committee) recommendation to approve UFT, the FDA declined to act on that recommendation. As a result, UFT is not available. We were very disappointed when the FDA decided not to accept the ODAC recommendation.

NSABP-C-09: Phase III randomized trial of CAPOX with or without intra-arterial FUDR in patients with liver-only metastases

This new trial is for patients with liver-only metastases that are removed or ablated. Patients will receive CAPOX with or without intra-arterial FUDR. The European data with CAPOX for patients with liver-only disease certainly influenced the decision of the hepatic surgeons to use CAPOX as the baseline therapy. The question being tested is the role of intra-arterial FUDR. I think the real challenge is to see if hepatic surgeons from different institutions with different concepts can work together to evolve a clinical trial.

NSABP-R-04: Phase III randomized trial comparing preoperative therapy with capecitabine or continuous infusion 5-FU with or without oxaliplatin in patients with rectal cancer

The trial will be modified to include a randomization to plus or minus oxaliplatin, to determine oxaliplatin's role in radiosensitization, achieving a pathologic complete response (pCR), preserving sphincters, and decreasing the local-regional event rate at three years. This will be a two-by-two trial comparing capecitabine to continuous infusion 5-FU with or without oxaliplatin.

Select publications

Andre T et al; Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. **Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer.** *N Engl J Med* 2004;350(23):2343-51. **Abstract**

Benson AB 3rd et al. **American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer.** *J Clin Oncol* 2004;22(16):3408-19. **Abstract**

Carmichael J et al. **Randomized comparative study of tegafur/uracil and oral leucovorin versus parenteral fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer.** *J Clin Oncol* 2002;20(17):3617-27. **Abstract**

Cassidy J et al. **Capecitabine (X) vs bolus 5-FU/leucovorin (LV) as adjuvant therapy for colon cancer (the X-ACT study): Efficacy results of a phase III trial.** *Proc ASCO* 2004;**Abstract 3501**.

Douillard JY et al. **Multicenter phase III study of uracil/tegafur and oral leucovorin versus fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer.** *J Clin Oncol* 2002;20(17):3605-16. **Abstract**

McKendrick JJ et al. **Capecitabine (X) is resource saving compared with i.v. bolus 5-FU/LV in adjuvant chemotherapy for Dukes' C colon cancer patients: Medical resource utilization (MRU) data from a large phase III trial (X-ACT).** *Proc ASCO* 2004;**Abstract 3578**.

Sargent DJ et al. **Disease-free survival (DFS) vs. overall survival (OS) as a primary endpoint for adjuvant colon cancer studies: Individual patient data from 12,915 patients on 15 randomized trials.** *Proc ASCO* 2004;**Abstract 3502**.

Scheithauer W et al; X-ACT Study Group. **Oral capecitabine as an alternative to i.v. 5-fluorouracil-based adjuvant therapy for colon cancer: Safety results of a randomized, phase III trial.** *Ann Oncol* 2003;14(12):1735-43. **Abstract**

Wolmark N et al. **A phase III trial comparing oral UFT to FULV in stage II and III carcinoma of the colon: Results of NSABP Protocol C-06.** *Proc ASCO* 2004;**Abstract 3508**.

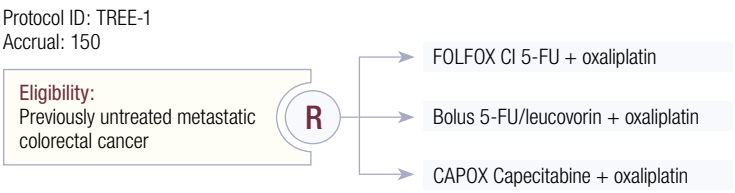
Wolmark N et al. **National Surgical Adjuvant Breast and Bowel Project trials in colon cancer.** *Semin Oncol* 2001;28(1 Suppl 1):9-13. **Abstract**

TREE trials: A comparison of three different oxaliplatin-containing regimens administered with or without bevacizumab

As far as we could tell from the Phase II and III studies conducted to date, there is significant activity of oxaliplatin with infusional 5-FU, bolus 5-FU or capecitabine. A huge study would be required to determine if one were better than the other; however, we believed significant toxicity differences could be observed in a smaller study. So, the TREE-1 trial looked at the three ways of administering oxaliplatin with a fluoropyrimidine (3.1) (Welles 2004).

After we accrued the first 150 patients to the TREE-1 trial, bevacizumab was shown to be effective in the pivotal trial with IFL. Therefore, we added bevacizumab to each of the three arms for the next 225 patients. Now, 375 patients have been randomly assigned to one of the three oxaliplatin-containing regimens administered with or without bevacizumab in a sequential design.

3.1 A Randomized Study of Three Oxaliplatin-Based Regimens as First-Line Therapy for Patients with Metastatic Colorectal Cancer



SOURCE: Welles L et al. **Preliminary results of a randomized study of the safety and tolerability of three oxaliplatin-based regimens as first-line treatment for advanced colorectal cancer (CRC) ("Tree" study).** *Proc ASCO* 2004;Abstract 3537.

It's not a true controlled randomized study of bevacizumab, but we will have comparative data for the different ways of administering the fluoropyrimidine

Dr Hochster is Professor of Medicine and Clinical Pharmacology at NYU Cancer Institute in New York, New York.

with oxaliplatin — 150 patients without bevacizumab and 225 patients with bevacizumab. We'll have some safety data to present at the ASCO GI meeting in January 2005 and a combined response analysis for ASCO in 2005.

The first thing we discovered in the TREE-1 trial was that the CAPOX regimen (oxaliplatin 130 mg/m^2 every three weeks and two weeks of capecitabine 1,000 mg/m^2 twice a day) was not well tolerated. We had a significantly higher incidence of diarrhea, dehydration, hospitalizations and dose reductions in that arm compared to the other arms. In October 2003, the Data Safety Monitoring Board (DSMB) recommended that the dose of capecitabine be reduced to 850 mg/m^2 twice a day for two weeks.

For the TREE-2 study, the lower capecitabine dose was used in combination with bevacizumab. As far as we know from the DSMB analysis, the toxicity associated with the addition of bevacizumab is pretty much what people would expect, based on the already-known data from the bolus IFL/bevacizumab study (Hurwitz 2004b) and ECOG-3200 (Giantonio 2004).

Phase II randomized trial of bevacizumab and cetuximab with or without irinotecan in patients with irinotecan-refractory disease

We're working with the New York Phase II consortium at Memorial Sloan-Kettering to complete a trial, with Leonard Saltz as the principal investigator, combining bevacizumab and cetuximab in patients whose disease has progressed on irinotecan. Patients are randomly assigned to receive both antibodies alone or both antibodies in combination with irinotecan.

This double-antibody study is a pilot trial for bringing both antibodies into the first-line setting. The patients on the study are tolerating the treatment very well. Even without irinotecan, the treatment seems to be holding the patients' disease or causing shrinkages. I don't know if or how much bevacizumab is adding to the cetuximab. The patients who receive the two antibodies alone have very minimal toxicity, except for skin rash.

First-line therapy in patients with metastatic disease

In a nonprotocol setting, I've been comfortable using an oxaliplatin-based regimen in combination with bevacizumab as first-line therapy for patients with metastatic disease, based on the TREE study and our own personal experience. The best data for improved time to progression, response rate and survival are with bevacizumab as first-line therapy, and I am most comfortable using oxaliplatin in the first-line setting. Therefore, I tend to use FOLFOX with bevacizumab in patients not enrolled on a protocol. We have seen nice responses and patients staying on those regimens for a long time.

Because of the issues with the dosing of capecitabine, concerns about compliance, and issues with diarrhea and hand-foot syndrome, I'm a little less likely to use capecitabine than a 5-FU infusion, unless the patient really objects to the infusion. We have patients we treat with CAPOX, and I'm conducting a study with a variation of the CAPOX regimen as first-line therapy. A role for

capecitabine definitely exists, but we're still learning how to use it most effectively in the United States.

Second- and third-line therapy for patients with metastatic disease who have received FOLFOX in combination with bevacizumab

If I start patients on FOLFOX plus bevacizumab, then second-line therapy becomes a bit of a question. No compelling data tells you exactly what to do in that setting. You could adopt FOLFIRI after FOLFOX, based on the European study by Chris Tournigand (Tournigand 2004) showing that the sequence for FOLFOX and FOLFIRI doesn't matter (3.2, 3.3).

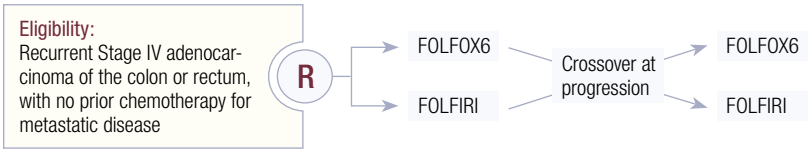
You could argue for the use of irinotecan alone. We know that 5-FU is synergistic with oxaliplatin from the second-line trial (Rothenberg 2003), but nobody has ever shown that with irinotecan. You might use irinotecan with cetuximab, even though that's not strictly within the FDA-approved indication. Additionally, you might use either regimen with bevacizumab, because if it's inhibiting angiogenesis or helping the chemotherapy enter the tumor, it probably would work as well in the second-line setting as in the first-line setting.

In general, based on the Tournigand data, I would tend to use FOLFIRI and probably continue bevacizumab, because I don't think there's a lot of additional toxicity. Of course, the risk of perforation and thrombotic events exists, but in otherwise healthy patients, I don't think that's a major risk. I think most patients are willing to accept that risk, if you discuss it with them.

Then, most often, I'll go on to a cetuximab regimen after using two lines of chemotherapy with bevacizumab. Based on the data from the two US studies (Saltz 2001, Saltz 2004) and the one randomized European study (Cunningham 2004), you're better off using irinotecan with cetuximab than cetuximab alone. The combination of cetuximab and irinotecan doubles the response rate and more than doubles the time to progression.

3.2 FOLFIRI Followed by FOLFOX6 or the Reverse Sequence in Advanced Colorectal Cancer

Protocol ID: FRE-GERCOR-C97-3/CPTF308
Accrual: 226 (Closed)



SOURCE: Tournigand C et al. *J Clin Oncol* 2004;22(2):229-37. **Abstract**

3.3 FOLFIRI Followed by FOLFOX6 or the Reverse Sequence: Objective Tumor Response Rates

	First-line		Second-line	
Event Rate	FOLFIRI (n=109)	FOLFOX6 (n=111)	FOLFOX6 (n=81)	FOLFIRI (n=69)
Overall response rate	56%	54%	15%	4%
Complete response	3%	5%	0%	0%
Partial response	53%	49%	15%	4%
Stable disease	23%	27%	48%	30%

Overall survival was 21.5 months and 20.6 months for FOLFIRI → FOLFOX and FOLFOX → FOLFIRI, respectively ($p = 0.99$).

SOURCE: Tournigand C et al. *J Clin Oncol* 2004;22(2):229-37. **Abstract**

Adjuvant therapy for patients with Stage II colon cancer

I've been a little disappointed with the failure of the colon cancer community to pick up on the results of the adjuvant therapy trials, especially combination chemotherapy for patients with Stage II disease. Those who treat breast cancer have known for a long time that adjuvant chemotherapy works just as well for patients with node-negative disease and that the relative benefit is about the same; it's just that the absolute benefit becomes smaller as the prognosis is better. If I see an otherwise healthy patient with Stage II colon cancer, I tend to offer them adjuvant FOLFOX.

If we were to treat all of the patients with Stage II colon cancer in the United States every year, we're talking about 3,000 lives saved. In breast cancer, patients and doctors are willing to accept more toxicity for a one percent difference; we aren't there yet in the colon cancer community.

I was very disappointed by the publication of the ASCO guidelines in the *Journal of Clinical Oncology* (Benson 2004), in which they did not recommend adjuvant therapy for patients with Stage II colon cancer. In Europe, it's accepted pretty widely and I think we should be moving in that direction.

X-ACT: Adjuvant capecitabine trial in patients with Dukes' C colon cancer

The X-ACT trial was a comparison of adjuvant capecitabine to the Mayo Clinic regimen. We now know adjuvant capecitabine is equal to or perhaps slightly better than the Mayo Clinic regimen (Cassidy 2004). I think that's a very important observation, and adjuvant capecitabine is a reasonable option for a well-educated patient who can be relied upon to take pills on a regular basis.

This requires a highly motivated patient who will call you or come in when they start to develop diarrhea, hand-foot syndrome or any of the toxicities. I don't

have a hesitation to use adjuvant capecitabine, based on the clinical data at this point in the adjuvant setting.

Clinical trials with cetuximab

I have experience with cetuximab going back to the original study, presented by Len Saltz, in patients with irinotecan-refractory disease who received irinotecan with cetuximab (Saltz 2001). The fact that adding cetuximab could make approximately 20 percent of the patients respond again and actually have measurable shrinkage was impressive. I believe cetuximab is going to be effective as first-line therapy. A trial from Europe is suggesting a high response rate in the first few patients treated with FOLFOX plus cetuximab as first-line therapy (Tabernero 2004). In a large randomized study — the EXPLORE trial — patients whose disease has progressed on irinotecan-containing regimens will be randomly assigned to FOLFOX with or without cetuximab. That study will enroll 1,100 patients.

Select publications

Benson AB 3rd et al. **American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer.** *J Clin Oncol* 2004;22(16):3408-19. **Abstract**

Cassidy J et al. **Capecitabine (X) vs bolus 5-FU/leucovorin (LV) as adjuvant therapy for colon cancer (the X-ACT study): Efficacy results of a phase III trial.** *Proc ASCO* 2004;**Abstract 3509**.

Cunningham D et al. **Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer.** *N Engl J Med* 2004;351(4):337-45. **Abstract**

Giantonio BJ et al. **The addition of bevacizumab (anti-VEGF) to FOLFOX4 in previously treated advanced colorectal cancer (advCRC): An updated interim toxicity analysis of the Eastern Cooperative Oncology Group (ECOG) study E3200.** *Proc ASCO* GI Symposium 2004; **Abstract 241**.

Hurwitz H et al. **Bevacizumab in combination with 5-fluorouracil and leucovorin: A promising regimen for first-line metastatic colorectal cancer.** *Proc ASCO* GI Symposium 2004;**Abstract 286**.

Hurwitz H et al. **Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.** *N Engl J Med* 2004;350(23):2335-42. **Abstract**

Rothenberg ML et al. **Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: Interim results of a phase III trial.** *J Clin Oncol* 2003;21(11):2059-69. **Abstract**

Saltz L et al. **Cetuximab (IMC-C225) plus irinotecan (CPT-11) is active in CPT-11-refractory colorectal cancer (CRC) that expresses epidermal growth factor receptor (EGFR).** *Proc ASCO* 2001;**Abstract 7**.

Saltz LB et al. **Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor.** *J Clin Oncol* 2004;22(7):1201-8. **Abstract**

Tabernero JM et al. **An international phase II study of cetuximab in combination with oxaliplatin/5-fluorouracil (5-FU)/folinic acid (FA) (FOLFOX-4) in the first-line treatment of patients with metastatic colorectal cancer (CRC) expressing Epidermal Growth Factor Receptor (EGFR). Preliminary results.** *Proc ASCO* 2004;**Abstract 3512**.

Tournigand C et al. **FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study.** *J Clin Oncol* 2004;22(2):229-37. **Abstract**

Welles L et al. **Preliminary results of a randomized study of the safety and tolerability of three oxaliplatin-based regimens as first-line treatment for advanced colorectal cancer (CRC) ("Tree" study).** *Proc ASCO* 2004;**Abstract 3537**.

Post-test:

Colorectal Cancer Update — Issue 1, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. The X-ACT adjuvant trial compared 5-FU/leucovorin and:
   a. FOLFOX4
   b. Capecitabine
   c. FOLFIRI
   d. All of the above
   e. None of the above

2. In the MOSAIC adjuvant trial, the addition of oxaliplatin resulted in a significant reduction in the risk of relapse.
   a. True
   b. False

3. Bevacizumab combined with IFL has been shown to prolong survival in the treatment of metastatic colorectal cancer.
   a. True
   b. False

4. A Phase II trial demonstrated capecitabine/oxaliplatin to be an active combination as first-line therapy for patients with metastatic colorectal cancer with an overall response rate of approximately:
   a. 15%
   b. 25%
   c. 40%
   d. 55%

5. NSABP-C-08 is an adjuvant trial that will compare adjuvant FOLFOX-6 with or without bevacizumab in patients with _____ colon cancer.
   a. Dukes' A
   b. Dukes' B
   c. Dukes' C
   d. Dukes' A or B
   e. Dukes' B or C

6. In the X-ACT trial, adjuvant capecitabine was at least as efficacious, if not more so, than the Mayo Clinic regimen of 5-FU/leucovorin in patients with Stage III colon cancer.
   a. True
   b. False

7. NSABP-C-09 will randomly assign patients with liver-only metastases that are ablated to:
   a. CAPOX
   b. Intra-arterial FUDR
   c. CAPOX alone or with intra-arterial FUDR

8. NSABP-R-04 will evaluate the role of preoperative capecitabine in patients with rectal cancer.
   a. True
   b. False

9. Clinical trials are evaluating the efficacy of cetuximab in combination with _____.
   a. Irinotecan
   b. Oxaliplatin
   c. Both a and b
   d. None of the above

10. The TREE trial compared which of the following fluoropyrimides in combination with oxaliplatin?
    a. Infusional 5-FU
    b. Bolus 5-FU
    c. Capecitabine
    d. Both a and c
    e. a, b and c

11. The trial by Tournigand and colleagues demonstrated that the sequence for FOLFOX and FOLFIRI is not important in terms of overall survival.
    a. True
    b. False

12. NSABP-C-06 demonstrated that disease-free and overall survival in patients treated with adjuvant oral UFT were _____ ____ disease-free and overall survival for patients treated with adjuvant leucovorin-modulated 5-FU.
    a. Better than
    b. Worse than
    c. Comparable to

Post-test Answer Key: 1b, 2a, 3a, 4d, 5e, 6a, 7c, 8a, 9c, 10e, 11a, 12c

Evaluation Form:

Colorectal Cancer Update — Issue 1, 2005

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion will be issued upon receipt of your completed evaluation form.

Please answer the following questions by circling the appropriate rating:

5 = Outstanding	4 = Good	3 = Satisfactory	2 = Fair	1 = Poor	N/A = not applicable to this issue of *CCU*

GLOBAL LEARNING OBJECTIVES

To what extent does this issue of *CCU* address the following global learning objectives?

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment and incorporate these data into management strategies in the local and advanced disease settings. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including the use of oxaliplatin- and capecitabine-containing regimens, and explain the absolute risks and benefits of adjuvant chemotherapy regimens to patients. . . . . 5 4 3 2 1 N/A
- Integrate emerging data on biologic therapies into management strategies for patients with advanced colorectal cancer. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Chris Twelves, MD	5 4 3 2 1	5 4 3 2 1
Norman Wolmark, MD	5 4 3 2 1	5 4 3 2 1
Howard S Hochster, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity . . . . . 5 4 3 2 1 N/A
Related to my practice needs . . . . . 5 4 3 2 1 N/A
Will influence how I practice . . . . . 5 4 3 2 1 N/A
Will help me improve patient care. . . . . 5 4 3 2 1 N/A
Stimulated my intellectual curiosity . . . . . 5 4 3 2 1 N/A
Overall quality of material . . . . . 5 4 3 2 1 N/A
Overall, the activity met my expectations. . . . . 5 4 3 2 1 N/A
Avoided commercial bias or influence . . . . . 5 4 3 2 1 N/A

Evaluation Form:

Colorectal Cancer Update — Issue 1, 2005

REQUEST FOR CREDIT — please print clearly

Name:..... Specialty:.....

ME No.:..... Last 4 Digits of SSN (required):.....

Street Address:..... Box/Suite:.....

City, State, Zip:.....

Telephone:..... Fax:.....

Email:.....

Research To Practice designates this educational activity for a maximum of 3.0 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature:..... Date:.....

Will the information presented cause you to make any changes in your practice?

☐ Yes ☐ No

If yes, please describe any change(s) you plan to make in your practice as a result of this activity:

.....

What other topics would you like to see addressed in future educational programs?

.....

What other faculty would you like to hear interviewed in future educational programs?

.....

Degree:

☐ MD ☐ PharmD ☐ NP ☐ BS ☐ DO ☐ RN ☐ PA ☐ Other.....

FOLLOW-UP

As part of our ongoing, continuous, quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

☐ Yes, I am willing to participate in a follow-up survey.

☐ No, I'm not willing to participate in a follow-up survey.

Additional comments about this activity:

.....

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Evaluation Form and mail or fax both to: Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131, FAX 305-377-9998. You may also complete the Post-test and Evaluation online at www.ColorectalCancerUpdate.com/CME.

Colorectal Cancer™ UPDATE

Editor	Neil Love, MD
Associate Editors	Michelle Paley, MD Richard Kaderman, PhD
Writers	Lilliam Sklaver Poltorack, PharmD Sally Bogert, RNC, WHCNP Douglas Paley Kathryn Ault Ziel, PhD
Content Validation	Margaret Peng
CME Director	Michelle Paley, MD
Art Director	Tamara Dabney
Senior Designer	Christina Brigham
Graphic Designers	Ben Belin Maria Schaefer
Production Editor	Aura Herrmann
Associate Production Editor	Alexis Oneca
Copy Editors	Sandy Allen Pat Morrissey/Havlin
Audio Production	Frank Cesarano
Technical Services	Arly Ledezma
Web Design	John Ribeiro
Production Coordinator	Cheryl Dominguez
Editorial Assistants	Patricia McWhorter Raquel Segura Tere Sosa Ginelle Suarez Arlene Thorstensen
Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: NLove@ResearchToPractice.net
For CME Information	Melissa Vives, Associate CME Administrator Email: MVives@ResearchToPractice.net

This program is supported by an education grant from Roche Laboratories Inc, Genentech BioOncology and Sanofi-Aventis.

Colorectal Cancer™

U P D A T E

This program is supported by education grants from
Roche Laboratories Inc, Genentech BioOncology and Sanofi-Aventis.

Research To Practice™

Sponsored by Research To Practice.

Last review date: January 2005
Release date: January 2005
Expiration date: January 2006
Estimated time to complete: 3 hours