Table of Contents

HOW TO USE THIS MONOGRAPH

This is a CME activity that 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** includes 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**.

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 FOR THE 2004 COLORECTAL CANCER UPDATE SERIES

Upon completion of this activity, participants should be able to:

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment.
- Counsel patients about the risks and benefits of adjuvant and neoadjuvant chemotherapy.
- Develop and explain a management strategy for patients with metastatic colorectal cancer.
- Describe ongoing clinical trials in colorectal cancer and counsel appropriately selected patients about the availability of ongoing clinical trials.

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 Ellis, Cunningham and Roh on the integration of emerging clinical research data into the management of colorectal cancer.

ACCREDITATION STATEMENT

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Lee M Ellis, MD	Grants/Research Support: ImClone Systems, AstraZeneca Pharmaceuticals LP Consultant: ImClone Systems, Attenuon LLC Honorarium: Genentech BioOncology
David Cunningham, MD, FRCP	Consultant and Honorarium: Sanofi Synthelabo Inc, Aventis Pharmaceuticals Inc, AstraZeneca Pharmaceuticals LP, Merck and Company Inc, Roche Laboratories Inc
Mark S Roh, MD	No financial interests or affiliations to disclose

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
bevacizumab	Avastin™	Genentech BioOncology
capecitabine	Xeloda®	Roche Laboratories Inc
cetuximab	Erbitux®	ImClone Systems, Bristol-Myers Squibb Company
dexamethasone	Various	Various
epoetin alpha	Procrit®	Ortho Biotech Products
floxuridine	Various	Various
5-fluorouracil, 5-FU	Various	Various
irinotecan	Camptosar®	Pfizer Inc
leucovorin	Various	Various
mitomycin	Mutamycin®	Bristol-Myers Squibb Company
	Mitomycin for Injection USP	Ben Venue Laboratories Inc
oxaliplatin	Eloxatin®	Sanofi-Synthelabo Inc
tegafur-uracil	Uftoral®	Bristol-Myers Squibb Company

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Editor's Note

A call to action

Several years ago we presented a case at the Miami Breast Cancer Conference that stands as a permanent testimonial to second opinions. The patient presented with a four-centimeter primary breast lesion and symptomatic metastatic disease. After chemo-therapy was administered, the breast lesion was reduced to one centimeter and the woman's symptoms abated.

Utilizing electronic keypad polling, we asked an audience of almost 1,000 physicians what they would recommend regarding surgery for the primary breast tumor. About one-fourth of the audience voted to do a mastectomy, one-half selected lumpectomy and the remaining quarter of attendees stated they would not recommend surgery.

The implications of this case are striking. Depending on which physician this patient visited, she might have had any one of three vastly different treatment options: no surgery, lumpectomy or mastectomy. I related this anecdote to Dr Mark Roh, a surgical oncologist interviewed for this issue of *Colorectal Cancer Update*, because there appears to be a similar disparity in treatment approaches to surgery for cancer of the rectum.

During the interview, Mark presented the case of a 63-year-old woman who sought a second opinion after being told she required an abdominoperineal (AP) resection and colostomy for a recently diagnosed rectal tumor. Dr Roh was not convinced that this was necessary, and he referred the patient to a medical oncologist for preoperative chemotherapy and radiation therapy.

This treatment resulted in an excellent tumor response. Mark was then able to remove the lesion without doing an AP resection. Today, the patient is free of cancer and has relatively normal bowel function. When I asked Mark how this experience affected this woman's perception of the medical community, he said, "It made her a believer in second opinions. She was alarmed that the physicians she had trusted for years would steer her down one road when it clearly was not the only road to travel. She was grateful that someone in her family suggested that she seek out other perspectives on how to treat the problem."

In interfacing with surgical and radiation oncologists for this series, it is apparent that this patient's story is far from unique. In an upcoming interview, Memorial Sloan-Kettering radiation oncologist Dr Bruce Minsky reiterates Dr Roh's concerns that many community-based surgeons overutilize AP resections, which results in thousands of patients receiving unnecessary colostomies every year.

What will it take to see this disturbing pattern change? Twenty years ago vocal breast cancer survivors, like Rose Kushner, stridently challenged the surgical

community to present lumpectomy as an option. In prostate cancer, the open stories of champions like General Norman Schwarzkopf and Andrew Grove have led to more discussion about nonsurgical treatment options. Will the same type of approach be required for cancer of the rectum? Will the social taboo of this disease prevent this from happening?

This is an appeal to all physicians who listen to or read this program. Is there someone in your practice who might be interested in "stepping up to the plate" and helping future patients?

Please let me know.

—Neil Love, MD
NLove@ResearchToPractice.net

Select publications

Bretagnol F et al. **Technical and oncological feasibility of laparoscopic total mesorectal excision with pouch coloanal anastomosis for rectal cancer.** *Colorectal Dis* 2003;5(5):451-3. **Abstract**

Crane CH et al. **The addition of continuous infusion 5-FU to preoperative radiation therapy increases tumor response, leading to increased sphincter preservation in locally advanced rectal cancer.** *Int J Radiat Oncol Biol Phys* 2003;57(1):84-9. **Abstract**

Crane CH, Skibber J. **Preoperative chemoradiation for locally advanced rectal cancer: Rationale, technique, and results of treatment.** *Semin Surg Oncol* 2003;21(4):265-70. **Abstract**

Guerrieri M et al. **Sphincter-saving surgery in patients with rectal cancer treated by radiotherapy and transanal endoscopic microsurgery: 10 years' experience.** *Dig Liver Dis* 2003;35(12):876-80. **Abstract**

McNamara DA, Parc R. **Methods and results of sphincter-preserving surgery for rectal cancer.** *Cancer Control* 2003;10(3):212-8. **Abstract**

Shirouzu K et al. **A new ultimate anus-preserving operation for extremely low rectal cancer and for anal canal cancer.** *Tech Coloproctol* 2003;7(3):203-6. **Abstract**

Tiret E et al. **Ultralow anterior resection with intersphincteric dissection – what is the limit of safe sphincter preservation?** *Colorectal Dis* 2003;5(5):454-7. **Abstract**

Tytherleigh MG, McC Mortensen NJ. **Options for sphincter preservation in surgery for low rectal cancer.** *Br J Surg* 2003;90(8):922-33. **Abstract**

Ueno H et al. **Preoperative parameters expanding the indication of sphincter preserving surgery in patients with advanced low rectal cancer.** *Ann Surg* 2004;239(1):34-42. **Abstract**

Errata

In our previous issue (Volume 2, Issue 4), Dr Patrick Flynn was misquoted in the print monograph as follows: "With bevacizumab, patients have to be willing to be on pumps." Bevacizumab administration does not require a continuous infusion pump. We regret this error.

Lee M Ellis, MD

Edited comments by Dr Ellis

Phase III trial of IFL with or without bevacizumab

Dr Hurwitz's presentation at ASCO 2003 underscores the importance of investigating new agents and combining them with standard chemotherapeutic approaches. The addition of bevacizumab, a monoclonal antibody to vascular endothelial growth factor (VEGF), to standard chemotherapy — irinotecan, 5-FU and leucovorin (IFL) — led to a significant improvement in median survival from 15.6 months to 20.3 months. This was the first Phase III randomized study to demonstrate a benefit with antiangiogenic therapy (Figure 1.1).

Figure 1.1

Efficacy Results from Phase III Trial of Bevacizumab (BV) in Combination with Bolus Irinotecan, 5-fluorouracil, Leucovorin (IFL) as First-Line Therapy in Patients with Metastatic Colorectal Cancer

	IFL/placebo (n=412)	IFL/BV (n=403)	*p*-value
Median survival (mo)	15.6	20.3	0.00003
Progression-free survival (mo)	6.24	10.6	<0.00001
Objective response rate (CR + PR)	35%	45%	0.0029
Duration of response (mo)	7.1	10.4	0.0014

SOURCE: 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.**

Mechanism of action of bevacizumab

Thirty years ago, Judah Folkman first proposed the hypothesis that blocking blood vessel growth might inhibit tumor growth, since all tumor cells require a nutrient blood supply. Antiangiogenic therapy (e.g., anti-VEGF agents) inhibits further blood vessel growth and tumor growth; it does not necessarily decrease tumor size, as expected with standard cytotoxic chemotherapy. Therefore, the 10 percent improvement in response rate with bevacizumab seen in Dr Hurwitz's study and in the study with capecitabine and bevacizumab in patients with breast cancer was quite surprising. Interestingly, George Sledge reported a nine percent

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response rate in a Phase I/II trial of single-agent bevacizumab in patients previously treated for breast cancer.

A more complete understanding of the biologic mechanisms that led to this improvement in response rate is needed. Blocking new blood vessel formation shouldn't necessarily improve the response rate, but it may improve time to progression or overall survival. Other mechanisms of action for the anti-VEGF agents should be sought.

Vascular endothelial growth factor and tumor blood flow

Vascular endothelial growth factor (VEGF) was discovered as a vascular permeability factor, and it's the most potent permeability factor we have discovered. Tumors express high levels of VEGF, which leads to leakiness of the microvasculature within tumors and leakage of plasma proteins and fluid into the interstitial spaces. Since most tumors don't have lymphatics, this fluid cannot re-enter the circulatory system. Therefore, interstitial pressure progressively increases as a tumor continues to grow — the larger the tumor, the greater the increase in interstitial pressure. As a consequence of this interstitial pressure, the lumens of blood vessels close off and blood flow is decreased, especially to the center of the tumor.

Some preclinical data suggest that anti-VEGF therapy may actually improve, rather than inhibit, blood flow to a tumor. It's difficult to destroy blood vessels within one or two days of administering an anti-VEGF agent; however, there are several preclinical and clinical studies demonstrating that an anti-VEGF agent can alter the vascular permeability in a tumor almost immediately. This suggests that anti-VEGF therapy may affect the vasculature in some other way, possibly by inhibiting permeability. If the permeability is inhibited, interstitial pressure within a tumor may also be inhibited, and the blood vessels may open up and improve blood flow.

Anti-VEGF therapy and chemotherapy uptake by tumors

If anti-VEGF therapy improves blood flow to the tumor, the delivery of chemotherapeutic agents may also improve. The same principle holds true for radiation therapy where oxygen is required to create free radicals. Mice that are pretreated with anti-VEGF therapy and then administered chemotherapy will have an increased uptake of chemotherapy into implanted tumors.

At the present time, it is not known whether certain chemotherapeutic agents will penetrate tumors better than others. Chemotherapeutic agents that are tightly bound to albumin may have limited access to the tumor tissues, whereas chemotherapeutic agents that are free in the plasma may penetrate the tumor tissue more readily. A preclinical study found increased irinotecan uptake by tumors implanted in mice that were pretreated with anti-VEGF therapy. Uptake of oxaliplatin by tumors implanted in mice that have been pretreated with anti-VEGF therapy has not been tested, but it is certainly of interest.

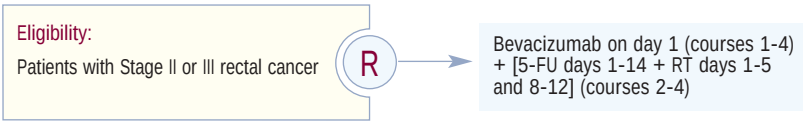
Controversy exists about whether the addition of bevacizumab to chemotherapeutic agents other than irinotecan will be equally beneficial. If anti-VEGF therapy truly improves delivery of chemotherapy by increasing blood flow to a tumor, it may not matter which chemotherapeutic agent is administered.

Bevacizumab and radiation therapy

Preclinical studies have shown that anti-VEGF therapy augments the effects of radiation therapy. Chris Willett, who originally hypothesized that interstitial pressure may impede the delivery of chemotherapy or oxygen to the tumor, is investigating the influence of bevacizumab on radiation therapy in patients with rectal cancer (Figure 1.2). In that trial, patients undergo baseline studies (e.g., MRI, CT scan, biopsies and measurement of interstitial tumor pressure) and initially receive bevacizumab alone for 14 days; then the studies are repeated. Bevacizumab is then continued, and 5-FU and radiation therapy are added. The study will determine whether there's any change in flow, interstitial pressure or response rate to chemoradiation therapy associated with bevacizumab.

Figure 1.2

Phase I Study of Neoadjuvant Bevacizumab, Fluorouracil and External Beam Radiotherapy in Patients with Stage II or III Rectal Cancer **Open Protocol**



Treatment repeats every 2 weeks for 4 courses in the absence of disease progression or unacceptable toxicity.
Patients undergo surgery 7 weeks after completion of chemoradiotherapy.
Cohorts of 6 patients receive escalating doses of bevacizumab until the maximum tolerated dose is determined.

Protocol IDs:	DFCI-02025, NCI-5642
Projected Accrual:	4-32
Study Contacts:	Christopher G. Willett MD, Protocol Chair Dana-Farber/Harvard Cancer Center at Dana-Farber Cancer Institute Tel: 617-724-1548; 877-726-5130

SOURCE: NCI, Physician Data Query, January 2004.

Bevacizumab in the management of metastatic colorectal cancer

Only Phase III clinical trials will determine whether the addition of bevacizumab to other chemotherapeutic agents will come to fruition. Many medical oncologists in academia have switched from IFL to FOLFIRI because its toxicity profile is better. It can be assumed that the addition of bevacizumab to FOLFIRI will give us the same results as the addition of bevacizumab to IFL, but this needs to be confirmed with a clinical trial.

At ASCO 2003, Rich Goldberg presented data demonstrating a median survival of 19.5 months with FOLFOX4, which is very similar to the median survival of 20.3 months seen with IFL plus bevacizumab. The choice between FOLFOX and IFL plus bevacizumab as first-line therapy will probably depend on the medical oncologist's practice and comfort level using oxaliplatin or antibodies.

Side effects associated with bevacizumab

Hypertension is the most consistent side effect and has been reported in as few as 20 percent and as many as 80 percent of patients treated with bevacizumab. It is postulated that hypertension may be a surrogate marker of biologic activity. Vascular endothelial growth factor causes induction of nitric oxide, which then causes vasodilation. Anti-VEGF therapy may block nitric oxide and produce a relative vasoconstriction. In the clinical trials, either stopping bevacizumab or increasing the dose of the patient's antihypertensive medication easily managed the hypertension. At times, another antihypertensive agent needed to be added, and it was very rare that patients were hospitalized for hypertension.

In the pivotal Phase III trial, six patients in the IFL plus bevacizumab arm and no patients in the IFL-alone arm experienced bowel perforation. The mechanism for the perforations is unknown. It is hypothesized that patients obtain such a good response to chemotherapy plus bevacizumab that their tumor, attached to the bowel, melts away. However, in reviewing the data, that does not appear to be the case. This is a toxicity that should be monitored in the future.

In some of the early bevacizumab trials, an increase in thrombosis and proteinuria was reported. However, in the large Phase III trial, there didn't appear to be any increase in thrombosis. Proteinuria was typically reversible upon cessation of the drug, but its long-term effect on the kidneys is unknown.

Select publications

Publications discussed by Dr Ellis

Cobleigh MA et al. **A Phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer.** *Semin Oncol* 2004;22(1):23-30. **Abstract**

Goldberg RM et al. **A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer.** *J Clin Onco* 2004;22(1):23-30. **Abstract**

Miller KD et al. **Phase III trial of capecitabine (Xeloda®) plus bevacizumab (Avastin™) versus capecitabine alone in women with metastatic breast cancer (MBC) previously treated with an anthracycline and a taxane.** *Breast Cancer Res Treat* 2002;76(Suppl 1);**Abstract 36**

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Wildiers H et al. **Effect of antivascular endothelial growth factor treatment on the intratumoral uptake of CPT-11.** *Br J Cancer* 2003;88(12):1979-86. **Abstract**

David Cunningham, MD, FRCP

Edited comments by Dr Cunningham

First-line therapy for metastatic disease

We've seen a major transformation in how we approach patients with metastatic disease over the past five to 10 years. Outcome has significantly improved, with average survival increasing from 6 to 7 months for patients who, in the past, didn't receive treatment for metastatic colorectal cancer, up to as much as 20 to 24 months. Most of that improvement can be attributed to the introduction of irinotecan and oxaliplatin into routine management of patients with metastatic disease.

Currently, in a nonprotocol setting, we tend to use combination chemotherapy as part of the first-line strategy. We usually combine capecitabine with oxaliplatin or irinotecan.

Capecitabine versus infusional 5-FU

The absolute purist would say you should use infusional 5-FU, either with oxaliplatin in the FOLFOX regimen or with irinotecan in the FOLFIRI regimen. At the Royal Marsden, we've been using infusional chemotherapy for more than 15 years, but we've moved away from it mainly because of patient preference and ease of administration of oral agents. The Phase II studies indicate a similar pattern of toxicity with capecitabine plus oxaliplatin or irinotecan compared to the infusional schedules, but without the need for placement of central lines or portacaths.

The majority of patients prefer an oral medication. Randomized trials comparing oral capecitabine or UFT with bolus 5-FU with a crossover between Cycle 1 and Cycle 2 have clearly shown that patients have a strong preference for the oral preparation.

Comparison of FOLFOX and FOLFIRI in the metastatic setting

It's difficult to choose between an irinotecan-based regimen and an oxaliplatin-based regimen, particularly in conjunction with either capecitabine or infusional 5-FU. The Phase III study conducted by Tournigand and his colleagues from France, comparing FOLFOX to FOLFIRI, didn't show much difference between

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the two regimens. Either regimen is acceptable, and the choice should be based on patient preferences. The North American Intergroup study comparing FOLFOX to IFL has resulted in a rapid change in practice.

Bevacizumab in the treatment of metastatic colorectal cancer

The data supporting the use of bevacizumab was generated by combining it with IFL. We'd all like the flexibility to use bevacizumab with a variety of combinations. The first one that comes to mind is FOLFIRI, which is clearly better tolerated than IFL and is probably more active. Second, we'd like the option of using bevacizumab with capecitabine and irinotecan (CAPIRI).

Of course, at the moment, we don't have any persuasive data suggesting that we should combine bevacizumab with the oxaliplatin-based regimen, although I think most people suspect that the biological effect observed in the bevacizumab randomized trial is less dependent upon irinotecan than just combining it with chemotherapy. The data with bevacizumab will radically alter how we approach the disease, and I think we all want to integrate it into the first-line strategy as soon as possible.

Clinical trial of cetuximab with or without irinotecan

At ASCO 2003, we presented the results of a randomized Phase II study of patients with metastatic disease whose tumors were resistant to irinotecan. Patients were randomly assigned to continue irinotecan and add in cetuximab, or to cetuximab alone. The rationale was to determine whether there was genuine synergistic activity between irinotecan and cetuximab or whether the response to cetuximab seen in prior studies was purely related to the cetuximab.

We found that approximately 20 percent of patients responded to the combination and approximately 10 percent responded to cetuximab alone. We also found significantly improved, progression-free survival in patients receiving the combination (approximately four months versus one-and-a-half months), although there was no impact on overall survival. This is partially due to a crossover effect; approximately 50 percent of patients randomly assigned to cetuximab alone went on to have irinotecan added if they either failed to respond or responded temporarily.

The MOSAIC and NSABP-C-07 adjuvant trials

We may be at another crossroads in colon cancer. At ASCO last year, Dr DeGramont presented the results of the MOSAIC adjuvant study, which randomized patients to 5-FU/LV versus 5-FU/LV and oxaliplatin. At three years, there was a significant improvement in disease-free survival in patients who received 5-FU/LV and oxaliplatin.

These data were received with great enthusiasm by the oncology community as the first good example in which two drugs were better than one in the adjuvant

treatment of colorectal cancer. There are some reservations about the trial, in that Dr De Gramont reported that the five percent difference in disease-free survival was likely to translate into an improved survival in the future. That's an area for debate. Some clinicians say, "That's good enough for me. I'm going to use FOLFOX in all my patients." Others say, "The data are interesting, but I prefer to us FOLFOX only in patients at higher risk."

The NSABP will report on trial C-07, comparing 5-FU with or without oxaliplatin as adjuvant therapy. Hopefully, C-07 will further reinforce the MOSAIC trial results. For patients at higher risk, with multiple positive nodes, I discuss the MOSAIC trial results. Some patients opt to receive the combination while others stick with 5-FU/LV in the absence of survival data.

Use of capecitabine in the adjuvant setting

We are awaiting the results of two large, randomized studies to determine whether oral agents can be substituted for 5-FU/LV in the adjuvant setting. NSABP-C-06 compares uracil/ftorafur (UFT) plus leucovorin to 5-FU/LV. The X-ACT trial is comparing the Mayo Clinic regimen of 5-FU/LV with capecitabine.

The data regarding administration and tolerability of capecitabine were presented by Christopher Twelves at ASCO last year and very much confirmed what we've seen in the advanced-disease setting. Capecitabine was well-tolerated, and I think most physicians believe it will be equivalent to 5-FU/LV.

If you're scientifically evaluating the evidence, you'd have to conclude that we need to wait for the data before using capecitabine in the adjuvant setting. I've been very open and clear with patients. I've told them, "We don't have definitive results, but most people think capecitabine and 5-FU/LV will be equivalent." On that basis, I have a number of patients who have elected to receive adjuvant capecitabine.

Capecitabine plus mitomycin for advanced colorectal cancer

Capecitabine is a prodrug of 5-FU, which is activated by three steps — the final one being thymidine phosphorylase (TP). It appears that TP is found at higher levels in tumor cells than in normal tissue, and this may enhance the conversion of capecitabine to 5-FU within the tumor cell. Mitomycin increases levels of TP within tumor cells, which might further enhance the effects of capecitabine.

At ASCO 2003, we reported data from two Phase II studies of capecitabine plus mitomycin (Figure 2.1). In the first study, patients who were unsuitable for standard combination chemotherapy received capecitabine and mitomycin as first-line treatment, and we had response rates of around 40 percent. In the second study, we evaluated the combination in patients who failed both 5-FU and irinotecan, and the response rate was approximately 17 percent. There are proposals to evaluate this combination in the UK in patients who failed both oxaliplatin- and irinotecan-based regimens.

As a nonprotocol treatment option for patients who do not have access to bevacizumab or cetuximab, it's certainly worth considering. Patients who have failed standard first- and second-line treatments are often desperate to receive any form of therapy.

Figure 2.1

Capecitabine Plus Mitomycin in Metastic Colorectal Cancer

	Previously untreated MCRC* (n=44)	5-FU and irinotecan-resistant** (n=23)
Objective response	45.4%	22.0%
Stable disease	26.6%	57.0%

*SOURCE: Watkins D et al. **Capecitabine and mitomycin-C: An active low toxicity first line therapy in metastatic colorectal cancer (MCRC).** *Proc ASCO* 2003;**Abstract 1109.**

SOURCE: Rao S et al. **Capecitabine and mitomycin-C (MMC) shows promising activity as a 3rd line agent in patients with metastatic colorectal carcinoma (MCRC) resistant to 5FU and irinotecan. *Proc ASCO* 2003;**Abstract 1286.**

Select publications.

Publications discussed by Dr Cunningham

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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.**

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Harba A et al. **Capecitabine/mitomycin C as salvage therapy in oxaliplatin and CPT11 refractory advanced colorectal carcinoma (ACRC).** *Proc ASCO* 2003;**Abstract 1335.**

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.**

Rao S et al. **Capecitabine and mitomycin-C (MMC) shows promising activity as a 3rd line agent in patients with metastatic colorectal carcinoma (MCRC) resistant to 5FU and irinotecan.** *Proc ASCO* 2003;**Abstract 1286.**

Tournigand C et al. **FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR Study.** *J Clin Oncol* 2004;[Epub ahead of print]

Twelves C et al. **Improved safety results of a ph III trial of capecitabine vs bolus 5-FU/leucovorin (LV) as adjuvant therapy for colon cancer (the X-ACT Study).** *Proc ASCO* 2003;**Abstract 1182.**

Watkins D et al. **Capecitabine and mitomycin-C: An active low toxicity first line therapy in metastatic colorectal cancer (MCRC).** *Proc ASCO* 2003;**Abstract 1109.**

Mark S Roh, MD

Edited comments by Dr Roh, MD

NSABP-R-04 rectal cancer trial: Pre-operative capecitabine and radiotherapy

Rationale and design

While continuous infusion 5-FU in conjunction with radiotherapy is superior to bolus 5-FU with radiotherapy, the need for an intravenous catheter can cause associated problems and be a "hassle." NSABP-R-04 is a preoperative rectal cancer trial designed to evaluate capecitabine versus continuous infusion 5-FU. Patients in one arm are treated with capecitabine — mimicking a continuous infusion — while those in the control arm are treated with a typical course of the infusional 5-FU. All patients receive the same radiotherapy preoperatively and undergo surgery after systemic therapy.

We chose to evaluate capecitabine in this trial primarily because of its convenience. In addition, capecitabine preferentially concentrates in tumors up to three times as much as in normal tissue. In the two larger randomized studies of previously untreated patients with metastatic colorectal cancer, capecitabine was superior to continuous 5-FU infusion.

We will be collecting and storing tissue as part of this study. I believe years down the road, when we understand the molecular biology of rectal cancer, this information may help us find a prognostic indicator at a molecular level.

Novel strategies for trial accrual

Although the NSABP is very robust and vigorous, we realized that as an organization we cannot complete R-04 alone. We just don't have that many surgeons. We needed to reach out and involve those individuals not typically involved in these trials. In designing this study, we gathered a group of colorectal surgeons to assess the questions that were important to them and to enlist their help with accrual. In addition, we approached the major cooperative groups — ECOG, SWOG, CALGB, NCCTG — to work together on patient accrual and to hopefully advance the care of patients with rectal cancer.

This collaboration led to an agreement that NSABP-R-04 would be the first segment of a multisegment approach to patients with rectal cancer. Each of the cooperative groups would contribute to the preoperative R-04 trial, and this trial would be an entry point to postoperative trials from participating groups.

Dr Roh is Professor of Surgery at Drexel University College of Medicine and Chairman of Surgery at the Allegheny General Hospital in Pittsburgh, Pennsylvania.

The protocol chairman, Bob Beart, is very well-respected and prominent in the colorectal community, and he has done a great job engendering the enthusiasm of his colleagues. In addition, to my knowledge there has not been a rectal trial that addressed the issues of colorectal surgeons or tried to elicit their participation. Hopefully, this will be a good experience in that regard.

NSABP-C-09: Intra-arterial plus systemic therapy for resected hepatic metastases

In 1999, Nancy Kemeny published the results of an institutional trial showing that patients with hepatic metastases who undergo liver resection and receive both intra-arterial and systemic chemotherapy have improved survival and a decreased rate of recurrent disease within the liver. This was very exciting, and while theoretically it makes sense, it was only a single institution trial. Based on this trial, we have designed NSABP-C-09, which is a multi-institutional Phase III trial evaluating chemotherapy after liver resection for colorectal liver metastases (Figure 3.1).

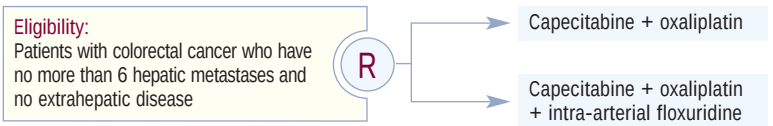
Patients who undergo resection or ablation (or both) of six or less hepatic metastases will be randomly assigned to a combination of intra-arterial and systemic therapy or systemic therapy alone. Both groups will receive oxaliplatin and capecitabine as the systemic component of their treatment. Half of the patients will also receive floxuridine intra-arterially.

Floxuridine has been around for many years, has a high hepatic extraction, and we've not found a better drug. In terms of the choice of capecitabine and oxaliplatin, we believe that capecitabine probably has efficacy at least equivalent to that of continuous infusion 5-FU. In addition, convenience was an issue. We believed that if the continuous infusion was too onerous for physicians, patients would not be enrolled in the study. With regard to the oxaliplatin, we tried to choose the best agent we could at the time, and we chose oxaliplatin over irinotecan.

Figure 3.1

Phase III Trial Comparing Intravenous Oxaliplatin and Oral Capecitabine and Hepatic Arterial Infusion of Floxuridine to Intravenous Oxaliplatin and Oral Capecitabine in Patients with Resected or Ablated Metastases to the Liver from Colorectal Cancer

Proposed Protocol



Protocol ID: NSABP-C-09
Projected Accrual: 400 patients

SOURCE: NSABP Annual Group Meeting, Orlando, Florida, June 26-29, 2003.

The NCCTG are conducting a very similar Phase II trial in which everyone has the catheter placed and receives the same regimen of systemic drugs — floxuridine intrahepatically and then capecitabine / oxaliplatin afterward (Figure 3.2) . Essentially, this is a Phase II study of what will be one arm of our study. They are trying to accrue 50 patients, and the understanding is that if we help them with their trial, they will help with ours.

Figure 3.2

Phase II Study of Hepatic Arterial Infusion with Floxuridine and Dexamethasone Followed by Systemic Therapy with Oxaliplatin and Capecitabine in Patients with Surgically Resected Liver Metastases from Primary Colorectal Carcinoma **Open Protocol**

Eligibility:
Patients with colorectal cancer who have hepatic metastases and no extrahepatic disease. Patients must have had prior surgical resection of the colorectal cancer and hepatic metastases.

PROTOCOL → (Intra-arterial floxuridine + dexamethasone) → oxaliplatin + capecitabine

Treatment repeats every six weeks for four courses in the absence of disease recurrence or unacceptable toxicity. After completion of the fourth course, patients receive oxaliplatin and capecitabine every three weeks for two courses in the absence of disease recurrence or unacceptable toxicity.

Protocol IDs:	NCCTG-N9945, NSABP-CI-66
Projected Accrual:	15-75 patients
Study Contacts:	North Central Cancer Treatment Group, Steven R Alberts, MD, Protocol Chair Tel: 507-284-4918 National Surgical Adjuvant Breast and Bowel Project, Roy E Smith, MD, Protocol Chair Tel: 412-330-4600

SOURCE: NCI, Physician Data Query, January 2004.

Surgical options for rectal cancer

Sphincter preservation and distance from the anal verge are key issues in determining the surgical procedure. The difficult cases are when the tumors are within three centimeters of the anal verge. The treatment of these patients is somewhat reflective of the experience of the surgeon. Some surgeons believe that is too close and that an abdominoperineal (AP) resection — a complete excision of the rectum, the distal rectum and the anus, requiring a permanent colostomy — is necessary.

A number of surgeons — and it's becoming more common — will excise almost down to the sphincter, and do a coloanal anastomosis to a pouch. The pouch maintains a reservoir so that patients are not going to the bathroom all the time. This procedure allows you to maintain oncologic principles, yet allows patients to resume somewhat more normal lifestyles than those who undergo AP resection.

In the best of hands, I believe the number of patients who undergo an AP resection is decreasing — probably down to approximately 10 percent. The surgeons I work with associate an AP resection as a sign of failure. But it is amazing and unfortunate that this is still the dominant procedure performed — probably 25 to 30 percent of patients with rectal cancer are having this type of procedure done. I believe that it will become less and less common as time goes on. My hope and expectation is that surgeons will become more adept at the pouch technique.

Management of hepatic metastases with surgical resection

In the evaluation and management of hepatic metastases, determination of resectability is critical. After confirmation that the disease is potentially resectable, extrahepatic disease must be ruled out by a thorough systemic evaluation. Assuming the patient has resectable disease on CAT scan and no evidence of extra-hepatic disease, surgical resection is the ideal next step, offering the best chance for cure. Resectable lesions should be treated surgically, and the unresectable lesions — deeper and riskier lesions — can be treated with nonresective methods like ablation.

There is a great deal of variability in how surgeons approach resection. One critical issue is margins. I'm constantly amazed at surgeons who basically shell out a tumor in the liver leaving a positive margin. Extensive data shows that a patient's survival with this approach is the same as if they had not undergone surgery. The other issue is the treatment of bilobar disease, which is very common. Some surgeons remove only the disease in one lobe, knowing that there is residual disease and anticipating further resection of the residual disease after hepatic regeneration has occurred. This approach makes no sense to me, as the liver regeneration occurring after the initial resection is almost like fertilizer for the remaining tumors.

When I began resecting liver metastases, most medical oncologists believed that only patients with one lesion should be considered for resection. This was based on well-established literature demonstrating that these patients have the best chance for cure. But as our techniques and results have improved, we can resect or ablate many more lesions — up to five or six. I believe more medical oncologists now consider whether resection or ablation is possible, even in patients with several lesions. These cases should at least be presented to a liver surgeon.

Select publications

Publications discussed by Dr Roh

Kemeny MM et al. **Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: Surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy—an Intergroup study.** *J Clin Oncol* 2002;20(6):1499-505. **Abstract**

Kemeny N et al. **Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer.** *N Engl J Med* 1999;341(27):2039-48. **Abstract**

Kemeny N et al. **Phase I/II study of hepatic arterial therapy with floxuridine and dexamethasone in combination with intravenous irinotecan as adjuvant treatment after resection of hepatic metastases from colorectal cancer.** *J Clin Oncol* 2003;21(17):3303-9. **Abstract**

Post-test: Colorectal Cancer Update, Issue 1, 2004

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **A Phase III randomized trial has demonstrated a significant improvement in survival for patients with metastatic colorectal cancer who were treated with bevacizumab plus:**
   a. 5-FU
   b. Oxaliplatin
   c. Irinotecan
   d. IFL
   e. FOLFOX

2. **It is hypothesized that anti-VEGF therapy will _____ the delivery of chemotherapy to the tumor.**
   a. Increase
   b. Decrease
   c. Not change
   d. Prevent

3. **Tumor markers are currently available to determine which patients will respond to bevacizumab.**
   a. True
   b. False

4. **NSABP-C-07 randomizes patients to 5-FU with or without**
   a. Irinotecan
   b. Capecitabine
   c. Oxaliplatin
   d. None of the above

5. **Capecitabine plus mitomycin is a low-toxicity combination that has activity in patients with metastatic colorectal cancer who were**
   a. Previously untreated
   b. 5-FU- and irinotecan-resistant
   c. a and b

6. **NSABP-R-04 will randomize patients to preoperative infusional 5-FU and radiotherapy versus:**
   a. Preoperative capecitabine and radiotherapy
   b. Preoperative oxaliplatin and radiotherapy
   c. Postoperative infusional 5-FU and radiotherapy
   d. Postoperative oxaliplatin and radiotherapy

7. **Hepatic resection should not be performed in patients with more than one liver metastasis.**
   a. True
   b. False

8. **Bowel perforation is the most common adverse event associated with bevacizumab.**
   a. True
   b. False

9. **Approximately 20 percent of patients with metastatic disease resistant to irinotecan responded to the combination cetuximab plus irinotecan in a Phase II trial.**
   a. True
   b. False

10. **NSABP trial C-09 for resected hepatic metastases will compare capecitabine plus oxaliplatin versus:**
    a. Capecitabine plus irinotecan
    b. Oxaliplatin plus irinotecan
    c. Capecitabine plus oxaliplatin plus intra-arterial floxuridine

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

Evaluation Form: Colorectal Cancer Update, Issue 1, 2004

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 is 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*	NA= *not applicable to this issue of CCU*

GLOBAL LEARNING OBJECTIVES FOR THE 2004 BREAST CANCER UPDATE SERIES

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 . . . . . 5 4 3 2 1 NA
- Counsel patients about the risks and benefits of adjuvant and neoadjuvant chemotherapy. . . . . 5 4 3 2 1 NA
- Develop and explain a management strategy for patients with metastatic colorectal cancer. . . . . 5 4 3 2 1 NA
- Describe ongoing clinical trials in colorectal cancer and counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 NA

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Lee M Ellis, MD	5 4 3 2 1	5 4 3 2 1
David Cunningham, MD, FRCP	5 4 3 2 1	5 4 3 2 1
Mark S Roh, 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
Related to my practice needs 5 4 3 2 1
Will influence how I practice 5 4 3 2 1
Will help me improve patient care 5 4 3 2 1
Stimulated my intellectual curiosity 5 4 3 2 1
Overall quality of material 5 4 3 2 1
Overall, the activity met my expectations 5 4 3 2 1
Avoided commercial bias or influence 5 4 3 2 1

Evaluation Form: Colorectal Cancer Update, Issue 1, 2004

Please Print Clearly

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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 on the activity.

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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.

_____

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

_____

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

_____

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Degree:

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

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.