CCU | 2006 VOL 5 | ISSUE 3

Colorectal Cancer™ UPDATE

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

EDITOR

Neil Love, MD

FACULTY

Edward Chu, MD

Robert A Wolff, MD

Howard A Burris III, MD

CME Certified

Download MP3 files of this audio program at ColorectalCancerUpdate.com

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 appropriate patients about the availability of ongoing clinical trials.
- Evaluate the emerging research data on various adjuvant chemotherapy approaches, including the use of oxaliplatin-containing regimens and the use of capecitabine or intravenous 5-FU, and explain the absolute risks and benefits of these regimens to patients.
- Evaluate emerging research data on various neoadjuvant radiation therapy/chemotherapy approaches to rectal cancer and explain the absolute risks and benefits of these 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 3 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Chu, Wolff and Burris 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 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

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** 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 **blue underlined text**.

TABLE OF CONTENTS

CONTENT VALIDATION AND DISCLOSURES

Research To Practice is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved by a peer review content validation process. The content of each activity is reviewed by both a member of the scientific staff and an external independent reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

The scientific staff and consultants for Research To Practice are involved in the development and review of content for educational activities and report the following real or apparent conflicts of interest for themselves (or their spouses/partners) that have been resolved through a peer review process: Richard Kaderman, PhD, Neil Love, MD, Mary Beth Nierengarten, Douglas Paley, Michelle Paley, MD, Margaret Peng, Lilliam Sklaver Poltorack, PharmD, Chris Thomson, MD, MS and Kathryn Ault Ziel, PhD — no real or apparent conflicts of interest to report; Marie Bialek, PharmD — freelance/contractor: McNeil Consumer & Specialty Pharmaceuticals, Janssen Pharmaceutica Products LP, Salary (spouse): AstraZeneca Pharmaceuticals LP; Sally Bogert, RNC, WHCNP — shareholder of Amgen Inc. Research To Practice receives education grants from Abraxis Oncology, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc, Biogen Idec, Genentech BioOncology, Genomic Health Inc, OSI Pharmaceuticals, Roche Laboratories Inc and Sanofi-Aventis, who have no influence on the content development of our educational activities.

In addition, the following faculty (and their spouses/partners) have reported real or apparent conflicts of interest that have been resolved through a peer review process:

Dr Chu — Consulting Fees: BMS-ImClone, Genentech BioOncology, Roche Laboratories Inc, Sanofi-Aventis. **Dr Wolff** — Consulting Fees: Eli Lilly and Company, Pfizer Inc. **Dr Burris** — Consulting Fees: Genentech BioOncology, Novartis Pharmaceuticals; Fees for Non-CME Services Received Directly from Commercial Interest or their Agents: 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 grantors.

UPCOMING EDUCATIONAL EVENTS

American College of Surgeons Oncology Group (ACOSOG) Semiannual Meeting
June 22-24, 2006
Chicago, Illinois
Event website: **acosog.org**

RTOG Semiannual Meeting
June 22-25, 2006
Toronto, Ontario
Event website: **rtog.org**

ECOG Semiannual Meeting
June 23-25, 2006
Washington, DC
Event website: **ecog.org**

NCCN Clinical Practice Guidelines Symposium: Colon, Rectal and Anal Cancers
June 24, 2006
New York, New York
Event website: **nccn.org**

UICC World Cancer Congress 2006
July 8-12, 2006
Washington, DC
Event website: **worldcancercongress.org**

NSABP Fall Meeting
October 13-16, 2006
Baltimore, Maryland
Event website: **nsabp.pitt.edu**

Second Annual Oncology Congress
October 19-21, 2006
New York, New York
Event website: **oncologycongress.com**

48th Annual Meeting of the American Society for Therapeutic Radiology and Oncology
November 5-9, 2006
Philadelphia, Pennsylvania
Event website: **astro.org**

EDITOR'S NOTE

Neil Love, MD

Son of FOLFOX

The highly informative and frequently entertaining National Surgical Adjuvant Breast and Bowel Project (NSABP) group meetings have always been among my favorite oncologic events. Over the years, I have spent many hours in the audience at these conferences listening intently to the discussion of ideas and concepts that would ultimately change the face of cancer treatment.

In the 80s and 90s Dr Bernard Fisher, who in the minds of many is the father of randomized clinical trials in cancer treatment, chaired these meetings and led the NSABP in a number of bold new directions. Today, Dr Norman Wolmark nobly carries forth this tradition of innovation, and the group's latest concept for their next adjuvant colon cancer trial (C-11), discussed at their most recent meeting in Denver the last weekend in April, exemplifies this tradition (1.1).

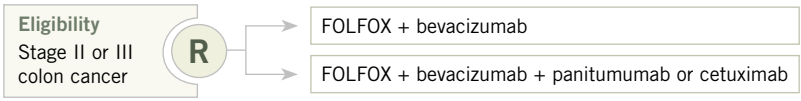
One of the most impressive aspects of the NSABP is its unique ability to get things done and done well. The group's trials ask simple yet critical questions and obtain answers expeditiously. The aforementioned new adjuvant trial proposed in Denver follows NSABP-C-08, which started out as a glimmer in Dr W's eye in June 2003 at the group's meeting in Orlando (1.2).

At that time, what was so impressive about the C-08 concept was that Dr Aimery de Gramont had presented the adjuvant FOLFOX data just a few weeks earlier at ASCO. Yet there was the NSABP — whose leadership anticipated the positive MOSAIC trials results — ready to take action.

1.1

Proposed Phase III Randomized Study of FOLFOX and Bevacizumab with or without Panitumumab or Cetuximab in Patients with Resected Stage II or III Colon Cancer

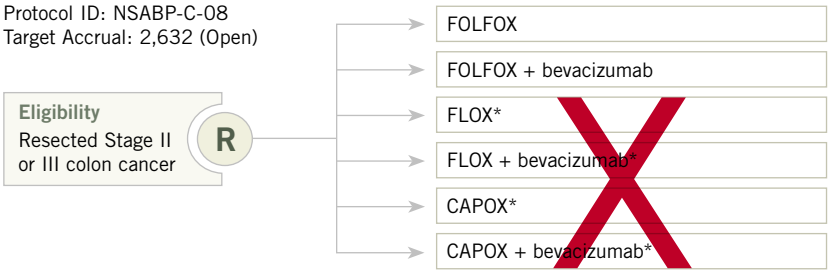
Protocol ID: NSABP-C-11



SOURCE: NSABP group meeting, April 2006.

1.2

Phase III Randomized Study of Adjuvant FOLFOX with or without Bevacizumab in Patients with Resected Stage II or III Colon Cancer*



* Arms three through six were initially proposed in June 2003 but later deleted

SOURCE: NSABP-C-08 Protocol, May 2006.

The proposed C-11 design is similarly forward thinking. Consider for a moment that the groundbreaking data in advanced colorectal cancer comparing panitumumab — a highly interesting humanized anti-EGFR monoclonal antibody — to best supportive care followed by panitumumab on progression had just been presented at the AACR meeting in Washington, DC a few weeks previously. Nonetheless, the NSABP's Dr Michael O'Connell was up at the podium considering adding this exciting agent to the presumed superior regimen in C-08.

Of even greater and certainly more immediate interest, at the meeting in Denver, Dr Wolmark updated the group on the status of C-08 and estimated that the trial will complete accrual in September! Having efficiently entered more than 2,000 people in about two years, the son of FOLFOX is ready for a new sibling.

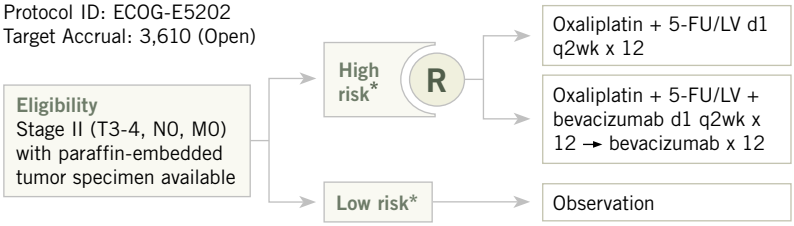
The spectacular results of the adjuvant trastuzumab breast cancer trials — including NSABP-B-31 — have suddenly raised our hopes that the future of oncology lies in a new generation of targeted treatment options that will provide major steps forward.

One particularly interesting aspect of trials like C-08 and C-11 is that patients have the opportunity to receive promising therapies — like bevacizumab, cetuximab and panitumumab — that would otherwise not be available to them in the adjuvant setting.

Although there can never be a guarantee of either safety or benefit, patients facing a significant risk of relapse despite our best interventions will eagerly embrace this new generation of trials. In fact, our CME group's recent survey of 150 colon cancer survivors demonstrated that 75 percent would have been willing (if eligible) to enter ECOG trial 5202 for patients with Stage II tumors (1.3), which evaluates the prognostic value of microsatellite instability, 18q deletions and FOLFOX with or without bevacizumab. (Now there's a familiar concept!)

1.3

Phase III Randomized Study of Oxaliplatin, Leucovorin Calcium and Fluorouracil with or without Bevacizumab in Patients with Resected Stage II Colon Cancer



* Patients are stratified according to disease stage (IIA versus IIB) and microsatellite stability (stable versus low-grade instability [MSI-L]). Patients at high risk for microsatellite instability (MSI) and loss of heterozygosity (LOH) at chromosome 18q are randomly assigned to one of two treatment arms (arms I and II), whereas patients at low risk for MSI and 18q LOH are assigned to arm III.

SOURCE: NCI Physician Data Query, May 2006.

Who could have imagined that in the span of 36 months, adjuvant therapy for colon cancer would have evolved from the old warhorse, 5-FU/leucovorin, to testing regimens that include a platinum compound, two biologic agents and an oral fluoropyrimidine prodrug?…The NSABP, that's who. Their next meeting is in Baltimore in October. More to come. ■

— Neil Love, MD
NLove@ResearchToPractice.net

SELECT PUBLICATIONS

Chau I, Cunningham D. **Adjuvant therapy in colon cancer — What, when and how?** *Ann Oncol* 2006;[Epub ahead of print]. **Abstract**

De Castro G Junior et al. **Angiogenesis and cancer: A cross-talk between basic science and clinical trials (the "do ut des" paradigm).** *Crit Rev Oncol Hematol* 2006;[Epub ahead of print]. **Abstract**

De Gramont A. **Rapid evolution in colorectal cancer: Therapy now and over the next five years.** *Oncologist* 2005;10(Suppl 2):4-8. **Abstract**

Ellis LM et al. **Overview of anti-VEGF therapy and angiogenesis. Part 1: Angiogenesis inhibition in solid tumor malignancies.** *Clin Adv Hematol Oncol* 2006;4(1):Suppl 1-10. **Abstract**

Goldberg RM et al. **Angiogenesis inhibition in the treatment of colorectal cancer Part 3 of a 3-part series: Targeting VEGF — Current and future research directions.** *Clin Adv Hematol Oncol* 2005;3(12):1-10. **Abstract**

Jain RK et al. **Lessons from phase III clinical trials on anti-VEGF therapy for cancer.** *Nat Clin Pract Oncol* 2006;3(1):24-40. **Abstract**

Love NH et al. **Patient perspectives on trade-offs of adjuvant systemic therapy for Stage II and III colon cancer: A survey of 150 people with colorectal cancer.** *Proc ASCO GI* 2006;**Abstract 373**.

Wainberg Z, Hecht JR. **A phase III randomized, open-label, controlled trial of chemotherapy and bevacizumab with or without panitumumab in the first-line treatment of patients with metastatic colorectal cancer.** *Clin Colorectal Cancer* 2006;5(5):363-7. No abstract available

INTERVIEW

Edward Chu, MD

Dr Chu is Professor of Medicine and Pharmacology, Chief of the Section of Medical Oncology and Deputy Director of Clinical Research at Yale School of Medicine's Cancer Center in New Haven, Connecticut.

Tracks 1-15

Select Excerpts from the Interview

Track 2

DR LOVE: What are the clinical implications of the MOSAIC adjuvant trial data?

DR CHU: It's clear that FOLFOX certainly provides significant clinical benefit to patients with Stage III disease, for whom oxaliplatin-based chemotherapy is FDA approved, but I also believe, based on the MOSAIC trial data, that patients with Stage II disease benefit significantly from FOLFOX (André 2004; de Gramont 2005; [2.1]).

At last year's ASCO meeting, Norm Wolmark presented the results from the NSABP adjuvant C-07 study, which demonstrated that a bolus 5-FU/leucovorin/oxaliplatin regimen — FLOX — also seemed to confer signifi-

cant clinical benefit (Wolmark 2005). We only have three-year disease-free survival data, but if one looks at the improvement with the bolus regimen of FLOX versus the infusional regimen of FOLFOX, they are virtually identical (2.2).

So for patients with a good performance status and very few comorbid illnesses, an oxaliplatin-based regimen is my first choice for adjuvant therapy.

For patients who are older and may have comorbid illnesses, the feeling is they might experience increased toxicity from oxaliplatin-based chemotherapy. In that setting fluoropyrimidine monotherapy is reasonable. Based on the results from the X-ACT trial (Twelves 2005), an oral fluoropyrimidine in the form of capecitabine is effective. If anything, based on the X-ACT trial, it appears to be more active and provide more clinical benefit than 5-FU/leucovorin, with a significantly improved safety profile.

2.1

Four-Year Follow-Up of the MOSAIC Adjuvant Trial Comparing FOLFOX4 to 5-FU/Leucovorin

	Absolute difference	Hazard ratio [95% CI]	*p*-value
Disease-free survival	**6.6%**	**0.77 [0.65-0.90]**	**<0.001**
Stage II	3.5%	0.82 [0.60-1.13]	NR
High-risk Stage II*	5.4%	0.76	NR
Stage III	8.6%	0.75 [0.62-0.89]	NR
Overall survival	**2.1%**	**0.91 [0.75-1.11]**	**NR**
Stage II	0	—	—
Stage III	3.2%	0.86[0.69-1.08]	NR

CI = confidence interval; NR = not reported; *T4, bowel obstruction, tumor perforation, poorly differentiated tumor, venous invasion and/or <10 examined lymph nodes

SOURCE: De Gramont A et al. Presentation. ASCO 2005;**Abstract 3501**.

2.2

Three-Year Disease-Free Survival (DFS) in NSABP-C-07 and MOSAIC

	Three-year DFS (oxaliplatin arm)	Absolute benefit from oxaliplatin	Hazard ratio	*p*-value
NSABP-C-07	76.5%	4.9%	0.79	<0.004
MOSAIC	78.2%	5.3%	0.77	0.002

SOURCES: Wolmark N et al. Presentation. ASCO 2005;**Abstract 3500**; André T et al. *N Engl J Med* 2004;350(23):2343-51. **Abstract**

Tracks 3-4

DR LOVE: How do you approach the dosing of capecitabine in the adjuvant and metastatic settings?

DR CHU: In the adjuvant setting, as per the X-ACT trial (Twelves 2005), the dose of capecitabine initially was 1,250 mg/m^2 twice a day on days one through 14 every 21 days. As it turned out, up to 42 percent of the patients required a dose reduction during the course of the trial. It's important to emphasize that approximately the same number of patients who were on 5-FU/leucovorin also required a dose reduction.

In the metastatic setting, where we're not attempting cure but rather palliation, the general experience has been to start patients at a lower dose — 900 to 1,000 mg/m^2 twice a day (for 14 of 21 days). In combination with either irinotecan or oxaliplatin, at least in the United States, the standard dose we're now thinking about is 800 to 850 mg/m^2 twice a day on days one through 14 every 21 days.

Track 5

DR LOVE: What is your approach to patients with Stage II disease?

DR CHU: It is not too different from my approach to patients with Stage III disease. If you look at the clinical studies and the analyses conducted thus far, there is growing evidence that adjuvant therapy for patients with Stage II colon cancer confers benefit, although the benefit is less than that seen in Stage III disease.

Out of every 100 patients with Stage II disease whom we treat, probably at most two to four patients may benefit, and among patients with Stage III disease, probably six to eight would benefit. In my practice, I tend to be fairly aggressive and have, in fact, offered FOLFOX to patients with Stage II disease. Recently, I was referred a patient who was a music professor at our university. They were concerned about the possibility of oxaliplatin-associated neuropathy as this individual was a pianist, so we used capecitabine.

Track 12

DR LOVE: Would you discuss the TREE-1 and TREE-2 studies and their implications for clinical practice?

DR CHU: The TREE-1 study was initially developed by Howard Hochster at NYU to evaluate the toxicity, safety profile and clinical activity of three different oxaliplatin-based regimens (Hochster 2005). One regimen was a modified FOLFOX-6. Another regimen was bolus 5-FU/leucovorin in combination with oxaliplatin that Howard developed, which had shown very promising results in the Phase II setting (Hochster 2003). The third regimen in TREE-1 was capecitabine with oxaliplatin.

When it became evident that bevacizumab was going to be approved by the FDA, the trial was then modified to the TREE-2 study. It involved the same three arms of oxaliplatin-based chemotherapy with the addition of bevacizumab.

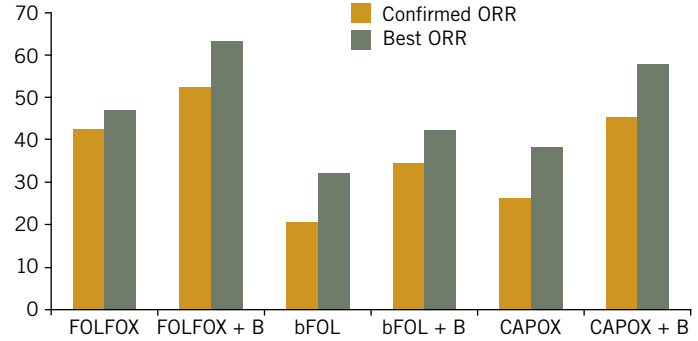
At the 2005 ASCO meeting, Howard reported that the bolus schedule was inferior in clinical activity and was associated with increased toxicity. The modified FOLFOX-6 and the CAPOX regimens were nearly identical, at least in terms of response rate, although it did seem that the modified FOLFOX-6 was slightly better (Hochster 2005; [2.3]).

DR LOVE: How are you approaching the selection of capecitabine versus 5-FU in combination with bevacizumab and oxaliplatin?

DR CHU: The TREE-2 study provides the rationale for substituting capecitabine for infusional 5-FU, and we're generally using CAPOX and bevacizumab. ■

2.3

Comparative Response Rates for TREE-1 and TREE-2



ORR = overall response rate; FOLFOX = infusional 5-FU/leucovorin and oxaliplatin
B = bevacizumab; bFOL = bolus 5-FU/leucovorin and oxaliplatin
CAPOX = capecitabine and oxaliplatin

SOURCE: Hochster HS et al. Poster. ASCO 2005;Abstract 3515.

SELECT PUBLICATIONS

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

De Gramont A et al. **Oxaliplatin/5FU/LV in the adjuvant treatment of Stage II and Stage III colon cancer: Efficacy results with a median follow-up of 4 years.** *Proc ASCO* 2005;Abstract 3501.

Hochster HS et al. **Safety and efficacy of bevacizumab (Bev) when added to oxaliplatin/fluoropyrimidine (O/F) regimens as first-line treatment of metastatic colorectal cancer (mCRC): TREE 1 & 2 Studies.** *Proc ASCO* 2005;Abstract 3515.

Hochster H et al. **Oxaliplatin with weekly bolus fluorouracil and low-dose leucovorin as first-line therapy for patients with colorectal cancer.** *J Clin Oncol* 2003;21(14):2703-7. Abstract

Twelves C et al. **Capecitabine as adjuvant treatment for stage III colon cancer.** *N Engl J Med* 2005;352(26):2696-704. Abstract

Wolmark N et al. **A phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: Results of NSABP protocol C-07.** *Proc ASCO* 2005;Abstract 3500.

INTERVIEW

Robert A Wolff, MD

Dr Wolff is Associate Professor of Medicine and Deputy Chairman for Clinical Affairs in the Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-18

Select Excerpts from the Interview

Track 6

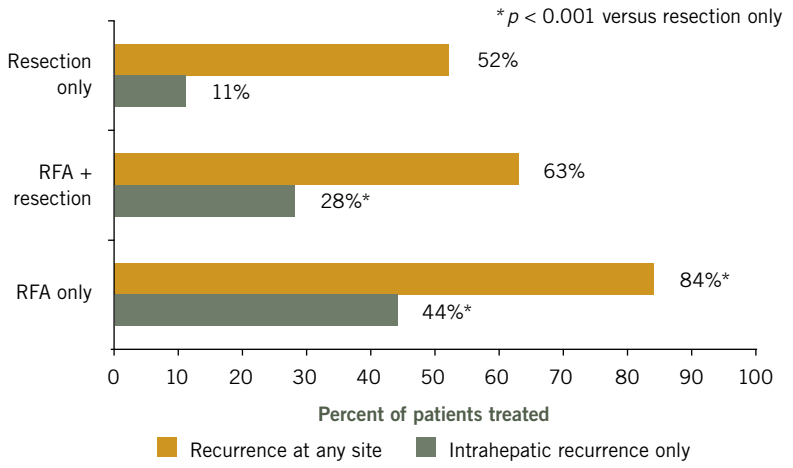
DR LOVE: Will you discuss the surgical treatment of colorectal metastases to the liver?

DR WOLFF: Steve Curley has published data for patients who have undergone

hepatic resection, hepatic resection combined with radiofrequency ablation or ablation only as the means to approach the metastatic component in the liver (Abdalla 2004). The patients who did best had a resection, and the patients who did worse had ablation only. Patients who had a combination of resection and ablation have intermediate results (3.1). So we're fans of resection whenever possible, if that's technically doable and we have enough hepatic remnant.

3.1

Tumor Recurrence in Patients with Colorectal Liver Metastases Treated with Hepatic Resection, Radiofrequency Ablation or Both



RFA = radiofrequency ablation

SOURCE: Abdalla EK et al. *Ann Surg* 2004;239(6):818-27. **Abstract**

Track 10

DR LOVE: What are your thoughts about using CAPOX as adjuvant treatment for colon cancer?

DR WOLFF: Enough data are available now that most authorities would say CAPOX and FOLFOX are almost equivalent. If they are not exactly the same in terms of efficacy, they are pretty close.

If we were talking about 5-FU versus capecitabine, a lot of physicians would favor capecitabine over a 5-FU program. This is an individual physician and patient choice, but I personally don't have any problems using capecitabine with oxaliplatin as part of the standard adjuvant treatment.

The logic would be that capecitabine is equivalent to 5-FU and leucovorin in the adjuvant setting, possibly a little bit better, and certainly less toxic.

FOLFOX is better than 5-FU and leucovorin in the adjuvant setting and,

therefore, I believe CAPOX is a reasonable adjuvant substitute.

DR LOVE: What about using CAPOX with bevacizumab?

DR WOLFF: That's a very attractive program, and this is a question the AVANT trial (3.2) will evaluate in the adjuvant setting: Would CAPOX with bevacizumab be equivalent to FOLFOX with bevacizumab? The most interesting question is whether bevacizumab adds anything in the adjuvant setting. Theoretically, if bevacizumab is an anti-angiogenic therapy, you might question how much benefit that drug could give you in the setting of microscopic metastatic disease.

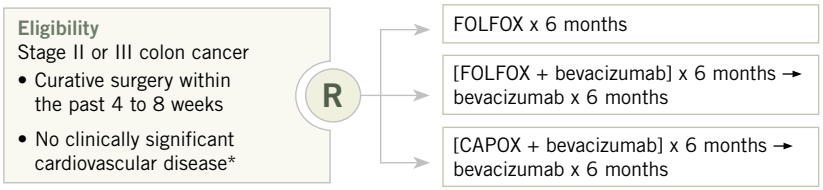
Lee Ellis has been a strong proponent that bevacizumab is not simply anti-angiogenic therapy; it's anti-VEGF therapy (Hicklin 2005; Ellis 2005). Data indicate that VEGF receptors are present on the tumor cells (Zhang 2002) and that VEGF may act as an autocrine growth factor for the tumor itself (Masood 2001).

So if you inhibit that pathway, you may obtain a greater benefit in the adjuvant setting. It will be interesting to see the data. Anybody who attempts to predict the result of that trial may be surprised. A difference may exist between bevacizumab and no bevacizumab, but I'll be surprised if a difference appears between FOLFOX/bevacizumab and CAPOX/bevacizumab.

3.2

AVANT Adjuvant Study: Phase III Randomized Trial Comparing FOLFOX to FOLFOX with Bevacizumab and CAPOX with Bevacizumab in Patients with Resected Colon Cancer

Target accrual: 3,450
Protocol IDs: UCLA-0412086-01, ROCHE-BO17920A, NCT00112918



* Cerebrovascular accident within the past 6 months; myocardial infarction within the past year; uncontrolled hypertension while on chronic medication; unstable angina; NYHA Class II-IV heart failure; serious cardiac arrhythmias that require medication

SOURCE: NCI Physician Data Query, May 2006.

Track 11

DR LOVE: Another situation in which capecitabine may be used in place of continuous-infusion 5-FU is the neoadjuvant treatment of rectal cancer with radiation therapy. What are your thoughts about that?

DR WOLFF: That's a very good question. One of the issues we need to recognize is that we can't study everything. We have to identify which research questions are the most important to answer.

I personally don't believe the question of whether capecitabine is superior, inferior or equivalent to infusional 5-FU or bolus 5-FU is so important to answer.

The Memorial group has data from preoperative rectal cancer demonstrating that whether you give patients bolus 5-FU with radiation therapy or infusional 5-FU with radiation therapy, the outcomes are equivalent.

The surprise came with the Intergroup trial, which showed infusional 5-FU as part of adjuvant therapy for rectal cancer was superior to bolus 5-FU (O'Connell 1994). Part of that may have been related to how much of the agent the patients in the bolus 5-FU arm received.

But if we accept the Memorial data — indicating no difference between bolus 5-FU and radiation therapy and infusional 5-FU with radiation therapy as part of a preoperative strategy — it's very likely that capecitabine will not be inferior to infusional or bolus 5-FU.

Track 14

DR LOVE: Would you discuss the neoadjuvant trial for patients with rectal cancer that you are currently conducting?

DR WOLFF: We are studying a combination of capecitabine, administered daily with bevacizumab, which will be administered every two weeks during the course of radiation therapy. Patients receive bevacizumab and capecitabine starting on the first day of the radiation and then receive bevacizumab every two weeks through radiation. After six weeks of rest, they are referred back to the surgeons, at which point the tumor is reevaluated.

This trial opened fairly recently. I've just had a patient complete it, and her disease has been downstaged from T3/N1 to T2/N0. ■

SELECT PUBLICATIONS

Abdalla EK et al. **Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases.** *Ann Surg* 2004;239(6):818-27. **Abstract**

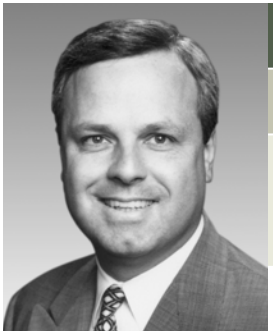
Ellis LM. **Bevacizumab.** *Nat Rev Drug Discov* 2005;Suppl:8-9. **Abstract**

Hicklin DJ, Ellis LM. **Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis.** *J Clin Oncol* 2005;23(5):1011-27. **Abstract**

Masood R et al. **Vascular endothelial growth factor (VEGF) is an autocrine growth factor for VEGF receptor-positive human tumors.** *Blood* 2001;98(6):1904-13. **Abstract**

O'Connell MJ et al. **Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery.** *N Engl J Med* 1994;331(8):502-7. **Abstract**

Zhang H et al. **Expression of vascular endothelial growth factor and its receptors KDR and Flt-1 in gastric cancer cells.** *World J Gastroenterol* 2002;8(6):994-8. **Abstract**



INTERVIEW

Howard A Burris III, MD

Dr Burris is Director of Drug Development at Sarah Cannon Research Institute in Nashville, Tennessee.

Tracks 1-19

Select Excerpts from the Interview

Track 3

DR LOVE: The difference in dosing of capecitabine in European versus North American studies has provoked much discussion. What did you observe in the X-ACT trial with the full dose of 2,500 mg/m^2 per day (in two doses, 14 days on, seven days off)?

DR BURRIS: A noticeable difference in dose reductions appeared between Europe and the United States, with far fewer dose reductions in Europe. If you

look at the trial as a whole, about 40 percent of the patients received a dose reduction. For American patients, the percentage was much higher.

Of the patients enrolled from our institution, almost 80 percent had their dose reduced. The fact that a higher percentage of Americans received a dose reduction may reflect that Americans have more leucovorin in their bodies because they are so well fed and well folated.

No variable other than location — including age, sex or size of the patients — was related to differences in dose reduction. American doctors were very quick to reduce dose at any sign of toxicity, and I believe they are certainly comfortable with lower doses of 2,000 mg/m^2. In the curves for the trial, the patients whose doses were reduced did just as well as those who remained at the full dose.

Track 4

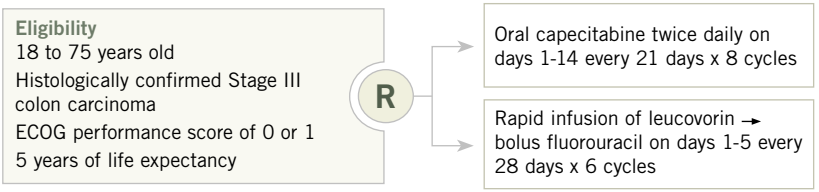
DR LOVE: Can you summarize the efficacy findings in the X-ACT study (4.1)?

DR BURRIS: Although it was designed to show noninferiority, the trial nearly showed superiority of capecitabine in the various endpoints studied. Time to relapse was significantly superior for capecitabine at the standard *p*-value of 0.05. A nonsignificant trend toward improved survival was also seen, with a *p*-value of 0.07.

For all three endpoints studied — disease-free, relapse-free and overall survival — capecitabine was about 15 percent better than the 5-FU arm (4.2). This translates into a small, incremental, four to five percent absolute benefit in each of those endpoints. So it was a "win" for capecitabine in that regard. In addition, because the *p*-values were powered for superiority and the trial was designed only to show noninferiority, this led to the FDA label expansion and the approval for capecitabine as adjuvant treatment for colon cancer.

4.1 **X-ACT Study: Oral Capecitabine versus Bolus Fluorouracil/Leucovorin**

Protocol ID: X-ACT
Accrual: 1,987 (Closed)



SOURCE: Twelves C et al. *N Engl J Med* 2005;352(26):2696-704. **Abstract**

Side effects and toxicity in the capecitabine arm were primarily diarrhea and hand-foot syndrome. Approximately 10 to 12 percent of patients experienced Grade III toxicities, but the side effects were quickly ameliorated by changes in dose and some dose delays.

4.2 Efficacy of Adjuvant Treatment in Stage III Colon Cancer: The X-ACT Trial

	Number of events over a median of 3.8 years			
	Capecitabine (n = 1,004)	5-FU/LV (n = 983)	HR (95% CI)	*p*-value E; S
DFS	348	380	0.87 (0.75-1.00)	<0.001; 0.05
RFS	327	362	0.86 (0.74-0.99)	—; 0.04
OS	200	227	0.84 (0.69-1.01)	<0.001; 0.07

E = equivalence; S = superiority; DFS = disease-free survival; RFS = relapse-free survival
OS = overall survival

SOURCE: Twelves C et al. *N Engl J Med* 2005;352(26):2696-704. **Abstract**

Track 11

DR LOVE: Clinically, can you detect a difference in the quality of responses you have observed with bevacizumab/chemotherapy compared to chemotherapy alone?

DR BURRIS: I've seen tremendous responses with the addition of bevacizumab, with near normalization or normalization of the CEAs, indicating the contribution of VEGF inhibition and possibly improved chemotherapy permeability to the tumors. Even more impressive is the degree of response. I've noticed in looking at CAT scans that 80 to 90 percent of the tumor is gone in those patients treated with the addition of bevacizumab to other agents, such as capecitabine, or regimens, such as FOLFOX.

DR LOVE: What's your typical first-line chemotherapy in a patient who's never had chemotherapy?

DR BURRIS: My typical front-line regimen is CAPOX with bevacizumab. If a patient walked into my clinic today, he or she would receive both oxaliplatin and bevacizumab every other week and capecitabine one week on, one week off (4.3). That regimen has gone well, with patients generally telling me that they feel good in the second week of therapy.

Track 12

DR LOVE: What is your approach to a patient who has an initial response with that regimen but has stopped oxaliplatin as a result of neuropathy and then has disease progression?

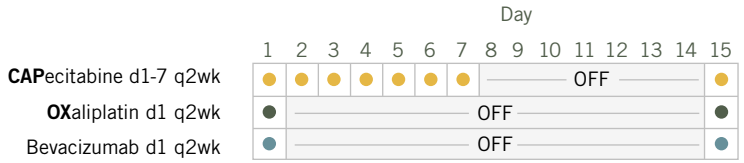
DR BURRIS: For the most part, those patients receive irinotecan-based therapy with bevacizumab if they are strongly EGFR-positive. I routinely test for this in patients with colon cancer, much like testing for estrogen receptor/progesterone receptor status in patients with breast cancer, so we have the EGFR data on our colon cancer patients from the beginning. If a patient is strongly EGFR-positive, I administer cetuximab with irinotecan.

DR LOVE: What about the combination of irinotecan, cetuximab and bevacizumab in that situation?

DR BURRIS: The data for that triplet are very encouraging (Saltz 2005; [4.4]). ■

4.3

A Regimen of CAPOX plus Bevacizumab as First-Line Therapy



SOURCE: Howard Burris III, MD, personal communication, February 2006.

4.4

BOND-2: Cetuximab/Bevacizumab with or without Irinotecan in Patients Who Have Failed Irinotecan

	Cetuximab/bevacizumab (n = 40)	Cetuximab/bevacizumab/ irinotecan (n = 41)
Partial response rate	20%	37%
Median time to progression	5.6 months	7.9 months

SOURCE: Saltz LB et al. Presentation. ASCO 2005. **Abstract 3508**

SELECT PUBLICATIONS

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**

Kelly H, Goldberg RM. **Systemic therapy for metastatic colorectal cancer: Current options, current evidence.** *J Clin Oncol* 2005;23(20):4553-60. **Abstract**

Meyerhardt JA, Mayer RJ. **Systemic therapy for colorectal cancer.** *N Engl J Med* 2005;352(5):476-87. No abstract available

Saltz LB et al. **Randomized phase II trial of cetuximab/bevacizumab/irinotecan (CBI) versus cetuximab/bevacizumab (CB) in irinotecan-refractory colorectal cancer.** *J Clin Oncol* 2005;23(16s):248. **Abstract 3508**

Twelves C et al. **Capecitabine as adjuvant treatment for stage III colon cancer.** *N Engl J Med* 2005;352(26):2696-704. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The improvement in three-year disease-free survival with FLOX for adjuvant therapy is comparable to that with FOLFOX.**
   a. True
   b. False

2. **The initial dose of capecitabine used in the X-ACT trial was _____.**
   a. 800 mg/m^2 twice a day on days one through 14 every 21 days
   b. 1,000 mg/m^2 twice a day on days one through 14 every 21 days
   c. 1,250 mg/m^2 twice a day on days one through 14 every 21 days
   d. 1,750 mg/m^2 twice a day on days one through seven and days 14 to 21 every four weeks
   e. All of the above

3. **The X-ACT trial demonstrated that patients who received capecitabine for adjuvant treatment of Stage III disease experienced advantages in _____ compared to those who received 5-fluorouracil/leucovorin.**
   a. Disease-free survival
   b. Relapse-free survival
   c. Both a and b

4. **In the TREE-2 study, the dose of capecitabine utilized was _____.**
   a. 1,250 mg/m^2 days one through 14 every three weeks
   b. 1,000 mg/m^2 days one through 14 every three weeks
   c. 850 mg/m^2 days one through 14 every three weeks

5. **In the TREE-2 study, the addition of bevacizumab improved overall response rates for _____.**
   a. Bolus 5-FU/leucovorin/oxaliplatin
   b. FOLFOX
   c. CAPOX
   d. All of the above

6. **Patients in the Phase III AVANT adjuvant study are randomly assigned to _____.**
   a. FOLFOX
   b. FOLFOX and bevacizumab
   c. CAPOX and bevacizumab
   d. All of the above

7. **The AVANT trial includes patients with high-risk Stage II or Stage III disease.**
   a. True
   b. False

8. **Exclusionary criteria for the AVANT trial include _____.**
   a. Myocardial infarction within the past year
   b. Unstable angina
   c. NYHA Class II-IV heart failure
   d. All of the above
   e. None of the above

9. **The BOND-2 trial compared cetuximab/bevacizumab with or without oxaliplatin for patients who failed irinotecan.**
   a. True
   b. False

10. **The NSABP-R-04 trial evaluates the efficacy of capecitabine or 5-fluorouracil with and without oxaliplatin as neoadjuvant treatment of resectable rectal cancer.**
    a. True
    b. False

11. **In a study by Abdalla and colleagues of patients with colorectal cancer metastatic to the liver, the best outcomes were observed using which of the following interventions?**
    a. Resection only
    b. Ablation only
    c. Resection and ablation
    d. None of the above

12 **In NSABP-C-07, 5-FU/leucovorin was administered as a(n) _____ in the FLOX regimen.**
    a. Infusion
    b. Bolus

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

EVALUATION FORM

Colorectal Cancer Update — Issue 3, 2006

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	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 appropriate patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging research data on various adjuvant chemotherapy approaches, including the use of oxaliplatin-containing regimens and the use of capecitabine or intravenous 5-FU, and explain the absolute risks and benefits of these regimens to patients. . . . . 5 4 3 2 1 N/A
- Evaluate emerging research data on various neoadjuvant radiation therapy/chemotherapy approaches to rectal cancer, and explain the absolute risks and benefits of these 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
Edward Chu, MD	5 4 3 2 1	5 4 3 2 1
Robert A Wolff, MD	5 4 3 2 1	5 4 3 2 1
Howard A Burris III, 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

Which of the following audio formats of this program did you use?

☐ Audio CDs ☐ Audio tapes ☐ Downloaded MP3s from website

EVALUATION FORM

Colorectal Cancer Update — Issue 3, 2006

REQUEST FOR CREDIT — please print clearly

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

Degree:

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

Medical License/ME Number: ..... 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 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation 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?

.....

Additional comments about this activity:

.....

FOLLOW-UP

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity 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 am not willing to participate in a follow-up survey.

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 ColorectalCancerUpdate.com/CME.

CCU306

Colorectal Cancer™ UPDATE

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	Email: CME@ResearchToPractice.net

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

Colorectal Cancer™

U P D A T E

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

Research To Practice®

Sponsored by Research To Practice.

Last review date: May 2006
Release date: May 2006
Expiration date: May 2007
Estimated time to complete: 3 hours